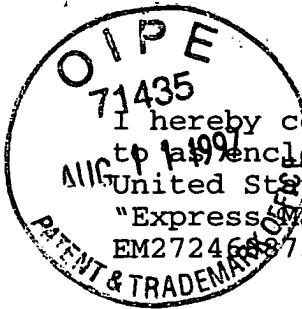


§/GAL/21



CERTIFICATION UNDER 37 CFR 1.10

I hereby certify that this paper and any documents referred  
to ~~as \$1.99~~ enclosed or attached are being deposited with the  
United States Postal Service on this date in an envelope as  
"Express Mail Post Office to Addressee" Mailing Label Number  
EM272468875US addressed to:

COMMISSIONER OF PATENTS AND TRADEMARKS

WASHINGTON, D.C. 20231

Attn: Box Patent Extension

on 8/11/97  
Date

SEP 5 1992

Bonnie Ferguson

Applicant: Chandraratna

Title: DISUBSTITUTED ACETYLENES BEARING HETEROAROMATIC AND  
HETEROBICYCLIC GROUPS HAVING RETINOID LIKE ACTIVITY

Allergan Docket: 16561CIP1(HL)

U.S. PATENT NO.: 5,089,509

ISSUED DATE: FEBRUARY 18, 1992

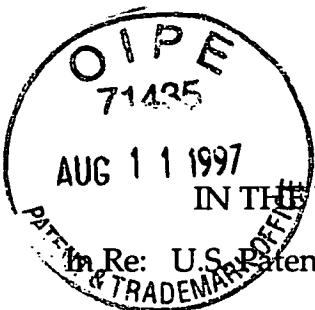
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Enclosed Are:

Certification Under 37 CFR 1.10 (Express Mail Label No.  
EM272468875US)

M19 - 2 1992  
PATENT EXTENSION  
A/C PATENTS

1. TRANSMITTAL LETTER
2. POSTCARD
3. DECLARATION /POWER OF ATTORNEY
4. APPLICATION FOR EXTENSION OF TERM UNDER 35 U.S. USC 156
5. ATTACHMENT A
6. ATTACHMENT B
7. ATTACHMENT C
8. ATTACHMENT D
9. ATTACHMENT E
10. ATTACHMENT F
11. ATTACHMENT G



DOCKET NO. 16561CIP1(HL)

PATENT

AUG 11 1997

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In Re: U.S. Patent No. 5,089,509

Issued: February 18, 1992

To: Roshantha Chandraratna

For: DISUBSTITUTED ACETYLENES BEARING  
HETEROAROMATIC AND HETEROBICYCLIC  
GROUPS HAVING RETINOID LIKE ACTIVITY

Commissioner of Patents and Trademarks  
Box Patent Extension  
Washington, D.C. 20231

Re: Allergan  
U.S. Patent No. 5,089,509

Sir:

Transmitted herewith is an application for extension of patent term under 35 U.S.C. 156 with regard to U.S. Patent No. 5,089,509. Two copies are submitted as duplicate originals.

Please charge Deposit Account No. 01-0885 in the amount of \$1,060. The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Account No. 01-0885. A duplicate of this sheet is enclosed.

Respectfully submitted,

ALLERGAN

By \_\_\_\_\_

Robert J. Baran  
Attorney for Applicant  
Registration No. 25,806

CERTIFICATE OF MAILING

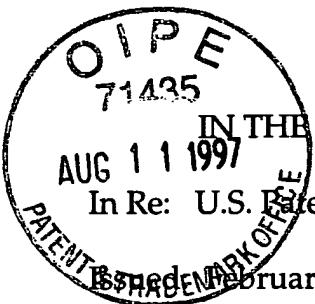
I HEREBY CERTIFY THAT THIS CORRESPONDENCE IS BEING DEPOSITED WITH THE UNITED STATES BOX PATENT EXTENSION, ASSISTANT COMMISSIONER FOR PATENTS, WASHINGTON, D.C. 20231 ON

August 11, 1997 (Date)

Name of person making deposit: Bonnie Ferguson

Signature: Bonnie Ferguson Date 8/11/97

04/08/1998 ACCORDING TO 37 CFR 1.10(b)(5) WITH SUFFICIENT POSTAGE AS EXPRESS MAIL IN AN ENVELOPE ADDRESSED TO:  
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DOCKET NO. 16561CIP1(HL)

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In Re: U.S. Patent No. 5,089,509

February 18, 1992

To: Roshantha Chandraratna

For: DISUBSTITUTED ACETYLENES BEARING  
HETEROAROMATIC AND HETEROBICYCLIC  
GROUPS HAVING RETINOID LIKE ACTIVITY

Commissioner of Patents and Trademarks  
Box Patent Extension  
Washington, D.C. 20231

August 11, 1997

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PATENT EXTENSION  
A/C PATENTS

APPLICATION FOR EXTENSION OF PATENT TERM UNDER 35 U.S.C. 156

Sir:

Allergan, a Texas Limited Partnership, (hereinafter "Applicant") hereby submits this application, under 35 U.S.C. §156, for extension of the term of United States Patent No. 5,089 509, by submitting this application pursuant to 37 CFR §1.740.

Applicant represents that it is the assignee of the entire interest in and to U.S. Patent No. 5,089,509, by virtue of the following:

U.S. Patent No. 5,089,509 issued on U.S. Patent Application 326,191, which was filed on March 20, 1989, and is a continuation in part of U.S. Patent Application Serial No. 246,037, which was filed on September 15, 1988, and is a continuation of U.S. Patent Application Serial No. 028,279, which was filed on March 20, 1987.

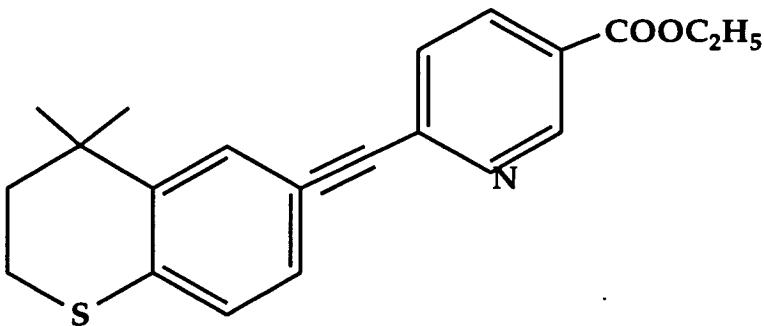
U.S. Patent Application Serial No. 028,279 was assigned by Roshantha Chandraratna to Allergan, Inc. on March 10,

1988, which assignment was recorded at Reel 4837, Frame 039 on February 8, 1988.

U.S. Patent Application Serial No. 326,191 was assigned to Allergan, Inc. by Roshantha Chandraratna on March 20, 1989, which assignment was recorded at Reel 5467, Frame 275 on October 9, 1990.

U.S. Patent No. 5,089,509 was assigned by Allergan, Inc. to Applicant, a wholly-owned subsidiary of Allergan, Inc., on January 17, 1996, which assignment was recorded at Reel 8239, Frame 0239 on May 6, 1996.

(1) The approved product (Tazorac<sup>®</sup>) is a topical formulation of the active ingredient, Tazarotene, which is ethyl 6-[2-(4,4-dimethylthiochroman-6-yl)ethynyl]nicotinate, and has the following structure:



Note the package insert for Tazorac<sup>®</sup> attached hereto as Exhibit A.

(2) Tazorac<sup>®</sup> a was subject to regulatory review under the Federal Food, Drug and Cosmetic Act, 21 U.S.C. § 355.

(3) Tazorac<sup>®</sup> received permission for commercial marketing for use in treating psoriasis or acne under Section 505 of the Federal Food, Drug and Cosmetic Act (21 U.S.C. § 355) on June 13, 1997.

(4) The active ingredient of Tazorac<sup>®</sup>, Tazarotene, has not previously been approved for commercial marketing under the Federal Food, Drug and Cosmetic Act, the Public Health Service Act, or the Virus-Serum-Toxin Act.

(5) This application for extension of patent term under 35 U.S.C. 156 is being submitted within the sixty (60) day period permitted for submission, the last permitted day for said submission being August 12, 1997.

(6) The complete identification of the patent for which an extension is being sought is as follows:

Inventor: Roshantha Chandraratna  
Patent No.: 5,089,509  
Issue Date: February 18, 1992  
Expiration Date: February 18, 2009

(7) A copy of the patent for which an extension is being sought is attached hereto as "Attachment B".

(8) No disclaimer, or Reexamination Certificate has been issued with respect to U.S. Patent No. 5,089,509. A Certificate of Correction was issued on June 21, 1994, a copy of which is attached hereto as "Attachment C". A copy of the Maintenance Fee Statement indicating payment of the Maintenance Fee, Fourth Year, in August of 1995, is attached hereto as "Attachment D".

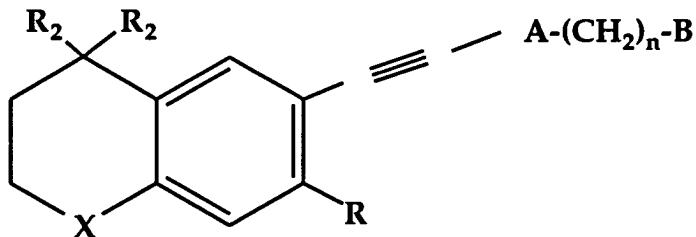
(9) U.S. Patent No. 5,089,509 claims the active ingredient of Tazorac<sup>®</sup>, Tazarotene, i.e., ethyl 6-[2-(4,4-dimethylthiochroman-6-yl)ethynyl]nicotinate, as identified in Paragraph (1) above. More specifically, claims 4 and 19 of this patent cover that compound as follows:

Claim 4 reads:

Ethyl 6-(2-(4,4-dimethylthiochroman-6-yl)ethynyl)nicotinate.

Claim 19 reads:

A method of treating psoriasis in a mammal which method comprises administering alone or in conjunction with a pharmaceutically acceptable excipient, a therapeutically effective amount of a compound of the formula



where X is S or O; R is hydrogen or lower alkyl; R<sub>2</sub> is methyl; A is pyridyl; n is 0-2; and B is H, -COOH or a pharmaceutically acceptable salt thereof, or an ester thereof with a saturated aliphatic alcohol of ten or fewer carbon atoms, or with a cyclic or saturated aliphatic cyclic alcohol of 5 to 10 carbon atoms, or with phenol or with a lower alkylphenol, or an amide or a mono or di-substituted amide thereof, the substituents on the amide being selected from a group consisting of saturated aliphatic radicals of ten or fewer carbon atoms, cyclic or saturated aliphatic cyclic radicals of 5 to 10 carbon atoms, and phenyl or lower

alkylphenyl radicals, or B is CH<sub>2</sub>OH or an ester derivative thereof derived from a saturated aliphatic acid of ten or fewer carbon atoms, or from a cyclic or saturate aliphatic cyclic acid of 5 to 10 carbon atoms, or from benzoic acid, or an ether derivative thereof derived from a saturated aliphatic radical of ten or fewer carbon atoms, or from a cyclic or saturated aliphatic cyclic radical of 5 to 10 carbon atoms, or from phenyl or lower alkylphenyl radical, or B is -CHO or a lower alkyl acetal derivative thereof, or an acetal derivative thereof formed with a lower alkyl diol, or B is -COR<sub>1</sub> or a lower alkyl ketal derivative thereof, or a ketal derivative thereof formed with a lower alkyl diol, where R<sub>1</sub> is -(CH<sub>2</sub>)<sub>m</sub>CH<sub>3</sub> where m is 0-4, or a pharmaceutically acceptable salt of the compound defined in said formula.

When X is S, R is hydrogen, A is pyridyl, n is 0, B is an ester derivative of -COOH and a saturated aliphatic alcohol of two carbon atoms, then ethyl 6-[2-(4,4-dimethylthiochroman-6-yl)ethynyl]nicotinate, the active ingredient for Tazorac<sup>®</sup>, is claimed for treating psoriasis.

(10) The relevant dates and information pursuant to 35 § U.S.C. 156(g) to enable the Secretary of Health and Human Services to determine the applicable regulatory review are as set forth in "Attachment E".

(11) A brief description of the activities undertaken by the Applicant during the applicable regulatory review period with respect to Tazorac<sup>®</sup> and the significant dates applicable to such activities is attached hereto as "Attachment F".

(12) A statement in accordance with 37 CFR § 1.740(a)(12) is attached hereto as "Attachment G".

(13) Applicant acknowledges a duty to disclose to the Commissioner of Patents and Trademarks and the Secretary of Health and Human Services any information which is material to any determination of entitlement to the extension sought.

(14) The prescribed fee for receiving and acting upon this Application for Extension is to be charged to Applicant's deposit account as authorized in the accompanying letter which is submitted in duplicate.

(15) Any inquiries and/or correspondence relating to this application for patent term extension should be directed to:

Mr. Robert J. Baran  
Allergan, Inc.  
2525 Dupont Drive  
Irvine, California 92612

(16) Applicant's attorney, undersigned, hereby certifies that this application is being submitted in duplicate originals.

(17) The requisite declaration under 37 CFR § 1.740 for extension of patent term under 35 U.S.C. § 156 is also attached hereto.

Respectfully submitted,

ALLERGAN



Robert J. Baran  
Attorney for Applicant  
Registration No. 25,806  
Telephone: 714/246-4669  
Telecopier: 714/246-4249

Allergan  
2525 Dupont Drive  
Irvine, CA 92612-1599

CERTIFICATE OF MAILING

I HEREBY CERTIFY THAT THIS CORRESPONDENCE IS BEING DEPOSITED WITH THE UNITED STATES POSTAL SERVICE WITH SUFFICIENT POSTAGE AS EXPRESS MAIL IN AN ENVELOPE ADDRESSED TO: BOX PATENT EXTENSION, ASSISTANT COMMISSIONER FOR PATENTS, WASHINGTON, D.C. 20231 ON August 11, 1997 (Date)

Name of person making deposit: Bonnie Ferguson

Signature: Bonnie Ferguson Date 8/11/97

# TAZORAC™

# ALLERGAN

Page 8  
∞ (tazaretene topical gel) 0.05%  
(tazaretene topical gel) 0.1%

## FOR DERMATOLOGIC USE ONLY NOT FOR OPHTHALMIC USE

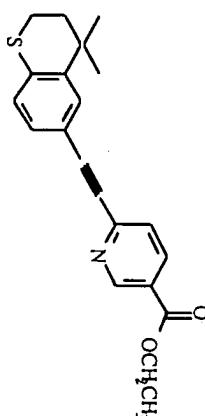
### DESCRIPTION:

TAZORAC™ is a translucent, aqueous gel and contains the compound tazarotene, a member of the acetylenic class of retinoids. It is for topical dermatologic use only. The active ingredient is represented by the following structural formula:

Molecular Weight: 351.46

Chemical Name:

ethyl 6-[2-(4,4-dimethylthio)chroman-6-yl]ethynyl] nicotinate



TAZAROTENE

C<sub>21</sub>H<sub>21</sub>NO<sub>2</sub>S

### Contains:

Active: Tazarotene . . . . . 0.05% or 0.1% (w/w)

Preservative: Benzyl alcohol . . . . . 1.0% (w/w)

Inactives: Ascorbic acid, butylated hydroxyanisole, butylated hydroxytoluene, carboner 934P, edetate disodium, hexylene glycol, purified water, poloxamer 407, polyethylene glycol 400, polysorbate 40, and tromethamine.

## ATTACHMENT A

keratinocyte cultures, it inhibits cornified envelope formation, whose build-up is an element of the psoriatic scale. The clinical significance of these findings is unknown. Acne: The mechanism of tazarotene action in acne is not defined. Tazarotene inhibited corneocyte accumulation in rhino mouse skin and cross-linked envelope formation in cultured human keratinocytes. The clinical significance of these findings is unknown.

### Pharmacokinetics:

Following topical application, tazarotene undergoes esterase hydrolysis to form its active metabolite, AGN 190299. Little parent compound could be detected in the plasma. AGN 190299 was highly bound to plasma proteins (>99%). Tazarotene and AGN 190299 were metabolized to sulfoxides, sulfones and other polar metabolites which were eliminated through urinary and fecal pathways. The half-life of AGN 190299 following topical application of tazarotene was similar in normal and psoriatic subjects, approximately 18 hours.

The human *in vivo* studies described below were conducted with tazarotene gel applied topically at approximately 2 mg/cm<sup>2</sup> and left on the skin for 10 to 12 hours. Both the peak plasma concentration (C<sub>max</sub>) and area under the plasma concentration time curve (AUC) refer to the active metabolite only.

Two single, topical dose studies were conducted using <sup>14</sup>C-tazarotene gel. Systemic absorption, as determined from radioactivity in the excreta, was less than 1% of the applied dose (without occlusion) in six psoriatic patients and approximately 5% of the applied dose (under occlusion) in six healthy subjects. One non-radio-labeled single-dose study comparing the 0.05% gel to the 0.1% gel in healthy subjects indicated that the C<sub>max</sub> and AUC were 40% higher for the 0.1% gel.

After 7 days of topical dosing with measured doses of tazarotene 0.1% gel on 20% of the total body surface without occlusion in 24 healthy subjects, the C<sub>max</sub> was 0.72 ± 0.58 ng/mL (mean ± SD) occurring 9 hours after the last dose, and the AUC<sub>0-24h</sub> was 10.1 ± 7.2 ng·hr/mL. Systemic absorption was 0.91 ± 0.67% of the applied dose.

In a 14-day study in five psoriatic patients, measured doses of tazarotene 0.1% gel were applied daily by nursing staff to involved skin without occlusion (8 to 18% of total body surface area; mean ± SD: 13 ± 5%). The C<sub>max</sub> was 12.0 ± 7.6 ng/mL occurring 6 hours after the final dose, and the AUC<sub>0-24h</sub> was 105 ± 55 ng·hr/mL. Systemic absorption was 14.8 ± 7.6% of the applied dose. Extrapolation of these results to represent dosing on 20% of total body surface yielded estimates of C<sub>max</sub> of 18.9 ± 10.6 ng/mL and AUC<sub>0-24h</sub> of 172 ± 88 ng·hr/mL.

An *in vitro* percutaneous absorption study, using radiolabeled drug and freshly excised human skin or human cadaver skin, indicated that approximately 4 to 5% of the applied dose was in the stratum corneum (tazarotene: AGN 190299 = 5:1) and 2 to 4% was in the viable epidermis-dermis layer (tazarotene: AGN 190299 = 2:1) 24 hours after topical application of the gel.

**Clinical Studies:**

**Psoriasis:**

In two large vehicle-controlled clinical studies, tazarotene 0.05% and 0.1% gels applied once daily for 12 weeks were significantly more effective than vehicle in reducing the severity of the clinical signs of stable plaque psoriasis covering up to 20% of body surface area. In one of the studies, patients were followed up for an additional 12 weeks following cessation of therapy with TAZORAC™. Mean baseline scores and changes from baseline (reductions) after treatment in these two studies are shown in the following Table:

**Plaque Elevation, Scaling and Erythema in Two Controlled Clinical Trials for Psoriasis**

N =	TAZORAC™ 0.05% Gel			TAZORAC™ 0.1% Gel			Vehicle Gel	
	Trunk/Arm/ Leg lesions	Knee/Elbow lesions	Trunk/Arm/ Leg lesions	Knee/Elbow lesions	Trunk/Arm/ Leg lesions	Knee/Elbow lesions		
Plaque elevation	B <sup>a</sup> C-12 <sup>b</sup> C-24 <sup>c</sup>	2.5 -1.4 -1.2	2.6 -1.3 -1.1	2.6 -1.1 -1.1	2.5 -1.4 -1.0	2.6 -1.5 -0.9	2.4 -0.8 -0.9	2.6 -0.7 -0.7
Scaling	B <sup>a</sup> C-12 <sup>b</sup> C-24 <sup>c</sup>	2.4 -1.1 -0.9	2.5 -1.1 -0.8	2.4 -0.9 -1.0	2.5 -1.3 -0.8	2.5 -1.2 -0.8	2.4 -0.7 -0.8	2.5 -0.6 -0.6
Erythema	B <sup>a</sup> C-12 <sup>b</sup> C-24 <sup>c</sup>	2.4 -1.0 -1.1	2.2 -0.8 -0.7	2.2 -0.9 -0.8	2.4 -1.0 -0.9	2.3 -1.1 -0.8	2.3 -0.8 -0.7	2.2 -0.5 -0.6

Plaque elevation, scaling and erythema scored on a 0-4 scale with:

• B = Mean Baseline Severity; C-12 = Mean Change from Baseline at end of 12 weeks of therapy;

C-24 = Mean Change from Baseline at week 24 (12 weeks after the end of therapy).

Global improvement over baseline at the end of 12 weeks of treatment in these two studies is shown in the following Table:

	TAZORAC™ 0.1% Gel			Vehicle Gel
	N=150	N=149	N=148	
Noninflammatory lesions	55%	43%	35%	27%
Inflammatory lesions	42%	47%	30%	28%
Total lesions	52%	45%	33%	27%

Global improvement over baseline at the end of 12 weeks of treatment in these two studies is shown in the following Table:

	TAZORAC™ 0.1% Gel			Vehicle Gel
	N=105	N=117	N=117	
100% improvement	1 (1%)	0	0	0
≥75% improvement	40 (38%)	21 (19%)	23 (20%)	11 (10%)
≥50% improvement	71 (68%)	56 (49%)	47 (40%)	32 (29%)
1-49% improvement	23 (22%)	49 (42%)	48 (41%)	46 (42%)
No change or worse	11 (10%)	12 (10%)	22 (19%)	32 (29%)

**INDICATIONS AND USAGE:**

TAZORAC™ (tazarotene topical gel) 0.05% and 0.1% are indicated for the topical treatment of patients with stable plaque psoriasis of up to 20% body surface area involvement.

TAZORAC™ (tazarotene topical gel) 0.1% is also indicated for the topical treatment of patients with facial acne vulgaris of mild to moderate severity. The efficacy of TAZORAC™ in the treatment of acne previously treated with other retinoids or resistant to oral antibiotics has not been established.

**CONTRAINDICATIONS:**

Retinoids may cause fetal harm when administered to a pregnant woman.

In rats, tazarotene 0.05%, administered topically during gestation days 6 through 17 at 0.25 mg/kg/day (1.5 mg/m<sup>2</sup>/day) resulted in reduced fetal body weights and

The 0.1% gel was more effective than the 0.05% gel, but the 0.05% gel was associated with less local irritation than the 0.1% gel (see ADVERSE REACTIONS section).

**Acne:**

In two large vehicle-controlled studies, tazarotene 0.1% gel applied once daily was significantly more effective than vehicle in the treatment of facial acne vulgaris of mild to moderate severity. Percent reductions in lesion counts after treatment for 12 weeks in these two studies are shown in the following Table:

**Reduction in Lesion Counts after Twelve Weeks of Treatment in Two Controlled Clinical Trials for Acne**

N =	TAZORAC™ 0.05% Gel			TAZORAC™ 0.1% Gel			Vehicle Gel	
	Trunk/Arm/ Leg lesions	Knee/Elbow lesions	Trunk/Arm/ Leg lesions	Knee/Elbow lesions	Trunk/Arm/ Leg lesions	Knee/Elbow lesions		
Plaque elevation	B <sup>a</sup> C-12 <sup>b</sup> C-24 <sup>c</sup>	2.5 -1.4 -1.2	2.6 -1.3 -1.1	2.5 -1.1 -1.1	2.6 -1.5 -1.0	2.4 -0.8 -0.9	2.6 -0.7 -0.7	2.6 -0.6 -0.6
Scaling	B <sup>a</sup> C-12 <sup>b</sup> C-24 <sup>c</sup>	2.4 -1.1 -0.9	2.5 -1.1 -0.8	2.4 -0.9 -1.0	2.5 -1.3 -0.8	2.5 -1.2 -0.8	2.4 -0.7 -0.8	2.5 -0.6 -0.6
Erythema	B <sup>a</sup> C-12 <sup>b</sup> C-24 <sup>c</sup>	2.4 -1.0 -1.1	2.2 -0.8 -0.7	2.2 -0.9 -0.8	2.4 -1.0 -0.9	2.3 -1.1 -0.8	2.3 -0.8 -0.7	2.2 -0.5 -0.6

Plaque elevation, scaling and erythema scored on a 0-4 scale with:

• B = Mean Baseline Severity; C-12 = Mean Change from Baseline at end of 12 weeks of therapy;

C-24 = Mean Change from Baseline at week 24 (12 weeks after the end of therapy).

reduced skeletal ossification. Rabbits dosed topically with 0.25 mg/kg/day (2.75 mg/m<sup>2</sup> total body surface area/day) tazarotene during gestation days 6 through 18 were noted with single incidences of known retinoid malformations, including spina bifida, hydrocephaly, and heart anomalies. As with other retinoids, when tazarotene was given orally to experimental animals, developmental delays were seen in rats, and teratogenic effects and post-implantation fetal loss were seen in rats and rabbits at doses producing 0.7 and 13 times, respectively, the systemic exposure (AUC<sub>0-24h</sub>) in human psoriasis patients, when extrapolated for topical treatment of 20% of body surface area. **THUS, SYSTEMIC EXPOSURE IN TOPICALLY TREATED PSORIASIS PATIENTS (FOR USE ON UP TO 20% OF BODY SURFACE AREA) COULD BE IN THE SAME ORDER OF MAGNITUDE AS IN THESE ORALLY TREATED ANIMALS.**

Systemic exposure anticipated in the treatment of facial acne may be less, due to a more limited area of application.

Six women inadvertently exposed to TAZORAC™ during pregnancy in clinical trials have subsequently delivered healthy babies. As the exact timing and extent of exposure in relation to the gestation time are not certain, the significance of these findings is not known.

TAZORAC™ is contraindicated in women who are or may become pregnant. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, treatment should be discontinued and the patient apprised of the potential hazard to the fetus. Women of child-bearing potential should be warned of the potential risk and use adequate birth-control measures when TAZORAC™ is used. The possibility that a woman of childbearing potential is pregnant at the time of institution of therapy should be considered. A negative result for pregnancy test having a sensitivity down to at least 50 mIU/mL for human chorionic gonadotropin (hCG) should be obtained within 2 weeks prior to TAZORAC™ therapy, which should begin during a normal menstrual period.

TAZORAC™ is contraindicated in individuals who have shown hypersensitivity to any of its components.

## WARNINGS:

**Pregnancy Category X.** See CONTRAINDICATIONS section. Women of childbearing potential should be warned of the potential risk and use adequate birth-control measures when TAZORAC™ is used. The possibility that a woman of childbearing potential is pregnant at the time of institution of therapy should be considered. A negative result for pregnancy test having a sensitivity down to at least 50 mIU/mL for hCG should be obtained within 2 weeks prior to TAZORAC™ therapy, which should begin during a normal menstrual period.

## PRECAUTIONS:

**General:** TAZORAC™ should only be applied to the affected areas. For external use only. Avoid contact with eyes, eyelids, and mouth. If contact with eyes occurs, rinse thoroughly with water. The safety of use over more than 20% of body surface area has not been established in psoriasis or acne.

Retinoids should not be used on eczematous skin, as they may cause severe irritation.

Because of heightened burning susceptibility, exposure to sunlight (including sunlamps) should be avoided unless deemed medically necessary, and in such cases, exposure should be minimized during the use of TAZORAC™. Patients must be warned to use sunscreens (minimum SPF of 15) and protective clothing when using TAZORAC™ until fully recovered. Patients with sunburn should be advised not to use TAZORAC™ until fully recovered. Patients who may have considerable sun exposure due to their occupation and those patients with inherent sensitivity to sunlight should exercise particular caution when using TAZORAC™ and ensure that the precautions outlined in the Information for Patients subsection are observed.

TAZORAC™ should be administered with caution if the patient is also taking drugs known to be photosensitizers (e.g., thiazides, tetracyclines, fluoroquinolones, phenothiazines, sulfonamides) because of the increased possibility of augmented photosensitivity.

If pruritus, burning, skin redness or peeling is excessive, the medication should be discontinued until the integrity of the skin is restored.

Weather extremes, such as wind or cold, may be more irritating to patients using TAZORAC™.

**Information for Patients:** See attached Patient Package Insert.

**Drug Interactions:** Concomitant dermatologic medications and cosmetics that have a strong drying effect should be avoided. It is also advisable to "rest" a patient's skin until the effects of such preparations subside before use of TAZORAC™ is begun.

**Carcinogenesis, mutagenesis, impairment of fertility:** Long-term studies of tazarotene following oral administration of 0.025, 0.050, and 0.125 mg/kg/day to rats showed no indications of increased carcinogenic risks. However, in other rat studies, oral doses twice that of the highest dose in the rat carcinogenicity study produced an AUC<sub>0-24h</sub> that was less (0.7 times) than that in topically treated psoriatic patients extrapolated for treatment of 20% of body surface area. In evaluation of photocarcinogenicity, median time to onset of tumors was decreased and the number of tumors increased in hairless mice following chronic topical dosing with intercurrent exposure to ultraviolet radiation at tazarotene concentrations of 0.001%, 0.005%, and 0.01% for up to 40 weeks.

A long-term topical application study in mice terminated at 88 weeks showed that dose levels of 0.05, 0.125, 0.25 and 1.0 mg/kg/day (reduced to 0.5 mg/kg/day for males after 41 weeks due to severe dermal irritation) revealed no apparent carcinogenic effects when compared to vehicle control animals; untreated control animals were not completely evaluated. The AUC<sub>0-12h</sub>'s for these doses were 82.7, 137, 183, 136 (males at 1.0/0.5 mg/kg) and 344 ng·hr/mL (females at 1.0 mg/kg), respectively. The mean AUC<sub>0-24h</sub> for psoriatic patients was 172 ng·hr/mL, extrapolated for 20% total body surface area.

Tazarotene was found to be non-mutagenic in the Ames assay and did not produce structural chromosomal aberrations in a human lymphocyte assay. Tazarotene was

also non-mutagenic in the CHO/Hprt mammalian cell forward gene mutation assay and was non-clastogenic in the *in vivo* mouse micronucleus test.

No impairment of fertility occurred in rats when male animals were treated for 70 days prior to mating and female animals were treated for 14 days prior to mating and continuing through gestation and lactation with topical doses of TAZORAC™ gel of up to 0.125 mg/kg/day (0.738 mg/m<sup>2</sup>/day).

Reproductive capabilities of F1 animals, including F2 survival and development, were not affected by topical administration of TAZORAC™ gel to female F0 parental rats from gestation day 16 through lactation day 20 at the maximum tolerated dose of 0.125 mg/kg/day (0.738 mg/m<sup>2</sup>/day).

**Pregnancy: Teratogenic Effects: Pregnancy Category X:** See CONTRAINDICATIONS section. Women of child-bearing potential should use adequate birth-control measures when TAZORAC™ is used. The possibility that a woman of childbearing potential is pregnant at the time of institution of therapy should be considered. A negative result for pregnancy test having a sensitivity down to at least 50 mIU/mL for hCG should be obtained within 2 weeks prior to TAZORAC™ therapy, which should begin during a normal menstrual period.

**Nursing mothers:** After single topical doses of <sup>14</sup>C-tazarotene to the skin of lactating rats, secretion of radioactivity was detected in milk, suggesting that there would be transfer of drug-related material to the offspring via milk. It is not known whether this drug is excreted in human milk. Caution should be exercised when tazarotene is administered to a nursing woman.

**Pediatric Use:** The safety and efficacy of tazarotene have not been established in pediatric patients under the age of 12 years.

**ADVERSE REACTIONS:**

**Psoriasis:**

The most frequent adverse events reported with TAZORAC™ 0.05% and 0.1% gels were limited to the skin. Those occurring in 10 to 30% of patients, in descending order, included pruritus, burning/stinging, erythema, worsening of psoriasis, irritation, and skin pain. Events occurring in 1 to 10% of patients included rash, desquamation, irritant contact dermatitis, skin inflammation, fissuring, bleeding and dry skin. Increases in "psoriasis worsening" and "sun-induced erythema" were noted in some patients over the 4th to 12th months as compared to the first three months of a 1 year study. In general, the incidence of adverse events with TAZORAC™ 0.05% gel was 2 to 5% lower than that seen with TAZORAC™ 0.1% gel.

**Acne:**

The most frequent adverse events reported with TAZORAC™ 0.1% gel were limited to the skin. Those events occurring in 10 to 30% of patients, in descending order, included desquamation, burning/stinging, dry skin, erythema and pruritus. Events occurring in 1 to 10% of patients included irritation, skin pain, fissuring, localized edema and skin discoloration.

In human dermal safety studies, tazarotene 0.05% and 0.1% gels did not induce contact sensitization, phototoxicity or photoallergy.

**OVERDOSAGE:**

Excessive topical use of TAZORAC™ may lead to marked redness, peeling, oil discomfort (see PRECAUTIONS).

TAZORAC™ is not for oral use. Oral ingestion of the drug may lead to the same adverse effects as those associated with excessive oral intake of Vitamin A (hypervitaminosis A) or other retinoids. If oral ingestion occurs, the patient should be monitored, and appropriate supportive measures should be administered as necessary.

**DOSAGE AND ADMINISTRATION:**

**General:** Application may cause a transitory feeling of burning or stinging. If irritation is excessive, application should be discontinued.

**For psoriasis:** Apply TAZORAC™ once a day, in the evening, to psoriatic lesions, using enough (2 mg/cm<sup>2</sup>) to cover only the lesion with a thin film to no more than 20% of body surface area. If a bath or shower is taken prior to application, the skin should be dry before applying the gel. Because unaffected skin may be more susceptible to irritation, application of tazarotene to these areas should be carefully avoided. TAZORAC™ was investigated for up to 12 months during clinical trials for psoriasis.

**For acne:** Cleanse the face gently. After the skin is dry, apply a thin film of TAZORAC™ (2 mg/cm<sup>2</sup>) once a day, in the evening, to the skin where acne lesions appear. Use enough to cover the entire affected area. TAZORAC™ was investigated for up to 12 weeks during clinical trials for acne.

**HOW SUPPLIED:**

TAZORAC™ (tazarotene topical gel) is available in concentrations of 0.05% and 0.1%. It comes in collapsible aluminum tubes, in 30 gm and 100 gm sizes.

	TAZORAC™ Gel 0.05%	TAZORAC™ Gel 0.1%
30 gm	NDC 0023-8335-03	NDC 0023-0042-03
100 gm	NDC 0023-8335-10	NDC 0023-0042-10

**NOTE:** TAZORAC™ gel should be stored at 25°C (77°F); excursion permitted to 15-30°C (59-86°F).

**CAUTION:** Federal (USA) law prohibits dispensing without prescription.

**ALLERGAN**  
Irvine, California 92612, USA

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# TAZORAC™



# ® ALLERGAN

{tazarotene topical gel} 0.05%  
(tazarotene topical gel) 0.1%

## INFORMATION FOR PATIENTS

Please read this leaflet carefully before you start to use your medicine. If you have any questions, or are not sure about anything, ask your doctor or pharmacist.

- The active ingredient in TAZORAC™ is tazarotene.

TAZORAC™ also contains benzyl alcohol as a preservative and the following inactive ingredients: ascorbic acid, butylated hydroxyanisole, butylated hydroxytoluene, carbomer 934P, edetate disodium, hexylene glycol, purified water, poloxamer 407, polyethylene glycol 400, polysorbate 40, and tromethamine.

## USES

TAZORAC™ 0.05% gel is used in the treatment of stable plaque psoriasis covering up to 20% of body surface area.

TAZORAC™ 0.1% gel is used in the treatment of stable plaque psoriasis covering up to 20% of body surface area and in the treatment of mild to moderately severe facial acne.

## BEFORE YOU USE THIS MEDICINE

You should be aware that:

- (a) TAZORAC™ should not be used if you are pregnant, attempting to become pregnant or at high risk of pregnancy. Consult your physician for adequate birth control measures if you are a female of child-bearing potential.
- (b) TAZORAC™ should be used with caution if you are also using other topical agents with a strong skin drying effect, products with high concentrations of alcohol, astringents, spices, the peel of lime, medicated soaps or shampoos, permanent wave solutions, electrolysis, hair depilatories or waxes, or other preparations or processes that might dry or irritate the skin, unless otherwise instructed by your health care practitioner.
- (c) TAZORAC™ should not be used if you have sunburn, eczema or other chronic skin condition(s). TAZORAC™ may cause severe irritation if applied to eczematous skin. If you have sunburn, you should wait until full recovery before using TAZORAC™.
- (d) TAZORAC™ should not be used if you are inherently sensitive to sunlight.

## HOW TO USE THIS PRODUCT:

- Read the directions on your prescription label carefully. Ask your doctor or pharmacist to explain anything that you do not understand.
- If you become pregnant while using TAZORAC™, you should immediately discontinue its use and contact your doctor.
- If you use a cream or lotion to soften or lubricate your skin, apply TAZORAC™ after ensuring that there is no more cream or lotion on the skin.
- After applying TAZORAC™, some people notice a feeling of itching, burning or stinging. This feeling may occur less often as your skin gets used to the medication. Consult your health care provider if increased sensitivity or irritation occurs.
- Do not cover treated areas with dressings or bandages.
- Never use more TAZORAC™ than instructed and never use it more often than instructed, as application of larger amounts of medication than

(e) TAZORAC™ should not be used if you are taking other drugs that increase your sensitivity to sunlight. Inform your physician if you are taking any other medications.

(f) You should use protective clothing and sunscreens with minimum SPF of 15 during the day when being treated with TAZORAC™. You should avoid direct sun exposure as much as possible and avoid sunlamps totally while being treated with TAZORAC™, unless advised otherwise by your doctor.

(g) If you have considerable sun exposure due to occupation, particular caution as described above should be exercised when using TAZORAC™.

(h) Weather extremes, such as wind or cold, may be more irritating to your skin while you are using TAZORAC™.

## BEFORE YOU USE THIS MEDICINE

Tell your doctor:

- (a) if you are pregnant or are considering becoming pregnant.
- (b) if you are breast-feeding.
- (c) if you are allergic to any ingredients in this medicine.
- (d) if you are already using other products that make your skin dry.
- (e) if you have a skin condition called eczema.
- (f) if you will be subject to excessive sun exposure.
- (g) if you are taking vitamin A supplements.

recommended will not lead to more rapid or better results, and marked redness, peeling or discomfort may occur.

- Wash your hands after applying the medication unless you are treating your hands for psoriasis. If the gel accidentally gets on areas you do not need to treat, wash it off.
- If TAZORAC™ comes in contact with your eyes, wash your eyes with large amounts of cool water, and contact a doctor if eye irritation persists.

#### **MISSED DOSES:**

- If you forget or miss a dose of TAZORAC™, do not try to "make it up." Return to your normal application schedule as soon as you can.

#### **INSTRUCTIONS SPECIFIC TO TREATMENT OF PSORIASIS:**

- If you bathe or shower before using TAZORAC™, be sure the skin is dry before application. Apply a thin film of the gel to your psoriasis lesions once a day before going to bed.
- Carefully avoid application to apparently uninvolved skin. TAZORAC™ may be more irritating to non-lesional skin.
- If you need to treat your hands, avoid contact with your eyes.

- Usually your psoriasis plaques and scales will begin to improve in about one to four weeks, but the redness may take longer to improve. Continue to use TAZORAC™ as directed by your doctor.
- Contact your doctor if your psoriasis becomes worse.

#### **INSTRUCTIONS SPECIFIC TO TREATMENT OF ACNE:**

- Gently clean and dry your face before using TAZORAC™. Apply TAZORAC™ once a day, before going to bed, to entire areas of the face where you have acne lesions. Use enough gel to cover the entire affected area with a thin film.
- Follow your doctor's directions for other routine skin care and the use of make-up. Talk to your doctor about the use of sunscreens and cosmetics, especially those that dry your skin.
- Usually your acne will begin to improve in about 4 weeks. Continue to use TAZORAC™ for up to 12 weeks as directed by your doctor.
- Contact your doctor if your acne becomes worse.

#### **WARNINGS:**

TAZORAC™ should not be used if you are pregnant, attempting to become pregnant or at high risk of pregnancy. Women of child-bearing potential should use adequate birth-control measures when TAZORAC™ is used.

If TAZORAC™ is swallowed by accident, contact your doctor or a poison control center.

Do not use TAZORAC™ after the expiration date found on the bottom seal of the tube.

This medicine is for your use only. It can only be prescribed by a doctor. Never give it to anyone else. It may harm them even if their skin problem appears to be the same as yours.

Retinoids should not be used on eczematous skin, as they may cause severe irritation. Do not use TAZORAC™ until your doctor has confirmed that your eczema has fully recovered.

Because of increased burning susceptibility, exposure to sunlight (including sunlamps) should be avoided or minimized during the use of TAZORAC™, unless prescribed differently by your doctor.

You should use sunscreens (minimum SPF of 15) and protective clothing when using TAZORAC™. Be certain that you use these precautions if you expect to experience considerable sun exposure or if you are sensitive to sunlight.

If you have a sunburn, do not use TAZORAC™ until you have fully recovered. Do not use TAZORAC™ if you are also taking drugs known to be photosensitizers (e.g., thiazides, tetracyclines, fluoroquinolones, phenothiazines, sulfonamides) unless you have discussed taking both drugs with your doctor, because of the increased possibility of a more severe reaction.

The safety of use over more than 20% of body surface area has not been established in psoriasis or acne.

**INSTRUCTIONS FOR USE AND HANDLING:** Keep tube tightly closed when not in use. Store it in a safe place where children cannot reach it. TAZORAC™ gel should be stored at 25°C (77°F); excursion permitted to 15-30 °C (59-86°F).

**IF YOU HAVE QUESTIONS ABOUT TAZORAC™ GEL:** You may contact Allergan by calling 800-433-8871.

**IF YOU HAVE QUESTIONS ABOUT PSORIASIS:** Information is available from:

The National Psoriasis Foundation:  
6600 SW 92nd Avenue, Suite 300, Portland, OR 97223-7195.  
Telephone: (800) 723-9166, or on the World Wide Web at <http://www.psoriasis.org>.

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# ATTACHMENT B

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US005089509A

United States Patent [19]  
Chandraratna

[11] Patent Number: 5,089,509  
[45] Date of Patent: Feb. 18, 1992

[54] DISUBSTITUTED ACETYLENES BEARING HETEROAROMATIC AND HETEROBICYCLIC GROUPS HAVING RETINOID LIKE ACTIVITY

[75] Inventor: Roshantha A. S. Chandraratna, El Toro, Calif.

[73] Assignee: Allergan, Inc., Irvine, Calif.

[21] Appl. No.: 326,191

[22] Filed: Mar. 20, 1989

#### Related U.S. Application Data

[63] Continuation-in-part of Ser. No. 246,037, Sep. 15, 1988, abandoned.

[51] Int. Cl.<sup>5</sup> ..... A61K 31/335; A61K 31/38; C07D 413/06; C07D 413/12

[52] U.S. Cl. ..... 514/337; 514/247; 514/269; 514/255; 514/432; 514/444; 514/456; 514/461; 514/863; 544/238; 544/333; 544/376; 549/13; 549/23; 549/60; 549/398; 549/425; 549/426; 549/427; 546/269; 546/274

[58] Field of Search ..... 546/269, 274; 514/337, 514/863

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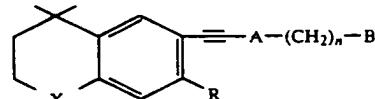
*J. Med. Chem.*, 1987, vol. 30, No. 8, pp. 1474-1482, Spruce et al.  
*J. Med. Chem.*, 1984, vol. 27, pp. 1516-1531, Dawson et al.

Primary Examiner—Johann Richter  
Attorney, Agent, or Firm—Gabor L. Szekeres; Martin A. Voet; Robert J. Baran

[57]

#### ABSTRACT

Retinoid-like activity is exhibited by compounds of the formula



where X is S, O, or NR' where R' is hydrogen or lower alkyl; R is hydrogen or lower alkyl; A is pyridyl, thiophenyl, furyl, pyridazinyl, pyrimidinyl or pyrazinyl; n is 0-2; and B is H, —COOH or a pharmaceutically acceptable salt, ester or amide thereof, —CH<sub>2</sub>OH or an ether or ester derivative, or —CHO or an acetal derivative, or —COR<sub>1</sub> or a ketal derivative where R<sub>1</sub> is —(CH<sub>2</sub>)<sub>m</sub>CH<sub>3</sub> where m is 0-4, or a pharmaceutically acceptable salt thereof.

19 Claims, No Drawings

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## DISUBSTITUTED ACETYLENES BEARING HETEROAROMATIC AND HETEROBICYCLIC GROUPS HAVING RETINOID LIKE ACTIVITY

This is a continuation-in-part of pending U.S. application Ser. No. 07/246,037 filed Sept. 15, 1988 now abandoned.

### BACKGROUND

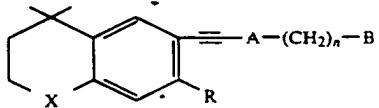
This invention relates to novel compounds having retinoid-like activity. More specifically, the invention relates to compounds having an ethynylheteroaromatic acid portion and a second portion which is a tetrahydroquinolinyl, thiocromanyl, or chromanyl group. The acid function may also be converted to an alcohol, aldehyde or ketone or derivatives thereof, or may be reduced to  $-\text{CH}_3$ .

### RELATED ART

Carboxylic acid derivatives useful for inhibiting the degeneration of cartilage of the general formula 4-(2-(4,4-dimethyl-6-X)-2-methylvinyl)benzoic acid where X is tetrahydroquinolinyl, chromanyl or thiocromanyl are disclosed in European Patent Application 0133795 published Jan. 9, 1985. See also European Patent Application 176034A published Apr. 2, 1986 where tetrahydronaphthalene compounds having an ethynylbenzoic acid group are disclosed.

### SUMMARY OF THE INVENTION

This invention covers compounds of formula I



wherein X is S, O, or NR' where R' is hydrogen or lower alkyl; R is hydrogen or lower alkyl; A is pyridinyl, thienyl, furyl, pyridazinyl, pyrimidinyl or pyrazinyl; n is 0-2; and B is H,  $-\text{COOH}$  or a pharmaceutically acceptable salt, ester or amide thereof,  $-\text{CH}_2\text{OH}$  or an ether or ester derivative, or  $-\text{CHO}$  or an acetal derivative, or  $-\text{COR}_1$  or a ketal derivative where  $R_1$  is  $-(\text{CH}_2)_m\text{CH}_3$  where m is 0-4.

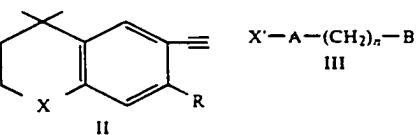
In a second aspect, this invention relates to the use of the compounds of formula I for treating dermatoses, such as acne, Darier's disease, psoriasis, ichthyosis, eczema, atopic dermatitis and epithelial cancers. These compounds are also useful in the treatment of arthritic diseases and other immunological disorders (e.g., lupus erythematosus), in promoting wound healing, in treating dry eye syndrome and in reversing the effects of sun damage to skin.

This invention also relates to a pharmaceutical formulation comprising a compound of formula I in admixture with a pharmaceutically acceptable excipient.

In another aspect, this invention relates to the process for making a compound of formula I which process comprises reacting a compound of formula II with a compound of formula III in the presence of cuprous iodide and  $\text{Pd}(\text{PQ}_3)_2\text{Cl}_2$  or a similar complex where the two formulas are represented by graphics II and III

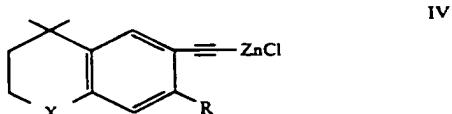
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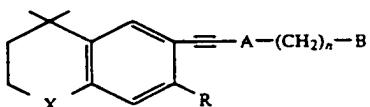
where X' is a halogen, preferably I; n and A are the same as defined above; and B is H, or a protected acid, alcohol, aldehyde or ketone, giving the corresponding compound of formula I; or to the process of making a compound of formula I which consists of reacting a zinc salt of formula IV with a compound of formula III in the presence of  $\text{Pd}(\text{PQ}_3)_4$  (Q is phenyl) or a similar complex,

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giving the corresponding compound of formula I; or homologating a compound of the formula

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where

n is 0-1 to give an acid of formula I; or converting an acid of formula I to a salt; or forming an acid addition salt; converting an acid of formula I to an ester; or converting an acid of formula I to an amide; or reducing an acid of formula I to an alcohol or aldehyde; or converting an alcohol of formula I to an ether or ester; or oxidizing an alcohol of formula I to an aldehyde; or converting an aldehyde of formula I to an acetal; or converting a ketone of formula I to a ketal.

### GENERAL EMBODIMENTS

#### Definitions

The term "ester" as used here refers to and covers any compound falling within the definition of that term as classically used in organic chemistry. Where A is  $-\text{COOH}$ , this term covers the products derived from treatment of this function with alcohols. Where the ester is derived from compounds where A is  $-\text{CH}_2\text{OH}$ , this term covers compounds of the formula  $-\text{CH}_2\text{OOCR}$  where R is any substituted or unsubstituted aliphatic, aromatic or aliphatic-aromatic group.

Preferred esters are derived from the saturated aliphatic alcohols or acids of ten or fewer carbon atoms or the cyclic or saturated aliphatic cyclic alcohols and acids of 5 to 10 carbon atoms. Particularly preferred aliphatic esters are those derived from lower alkyl acids and alcohols. Here, and where ever else used, lower alkyl means having 1-6 carbon atoms. Also preferred are the phenyl or lower alkylphenyl esters.

Amide has the meaning classically accorded that term in organic chemistry. In this instance it includes

# ATTACHMENT B (cont'd)

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the unsubstituted amides and all aliphatic and aromatic mono- and di-substituted amides. Preferred amides are the mono- and di-substituted amides derived from the saturated aliphatic radicals of ten or fewer carbon atoms or the cyclic or saturated aliphatic-cyclic radicals of 5 to 10 carbon atoms. Particularly preferred amides are those derived from lower alkyl amines. Also preferred are mono- and di-substituted amides derived from the phenyl or lower alkylphenyl amines. Unsubstituted amides are also preferred.

Acetals and ketals includes the radicals of the formula —CK where K is (—OR)<sub>2</sub>. Here, R is lower alkyl. Also, K may be —OR<sub>1</sub>O— where R<sub>1</sub> is lower alkyl of 2-5 carbon atoms, straight chain or branched.

A pharmaceutically acceptable salt may be prepared for any compound of this invention having a functionality capable of forming such salt, for example an acid amine functionality. A pharmaceutically acceptable salt may be any salt which retains the activity of the parent compound and does not impart any deleterious or untoward effect on the subject to which it is administered and in the context in which it is administered.

Such a salt may be derived from any organic or inorganic acid or base. The salt may be a mono or polyvalent ion. Of particular interest where the acid function is concerned are the inorganic ions, sodium, potassium calcium, and magnesium. Organic amine salts may be made with amines, particularly ammonium salts such as mono-, di- and trialkyl amines or ethanol amines. Salts may also be formed with caffeine, tromethamine and similar molecules. Where there is a nitrogen sufficiently basic as to be capable of forming acid addition salts, such may be formed with any inorganic or organic acids or alkylating agent such as methyl iodide. Preferred salts are those formed with inorganic acids such as hydrochloric acid, sulfuric acid or phosphoric acid. Any of a number of simple organic acids such as a mono-, di- or tri-acid may also be used.

The preferred compounds of this invention are those where the ethynyl group and the B group are attached to the 2 and 5 positions respectively of a pyridine ring (the 6 and 3 positions in the nicotinic acid nomenclature being equivalent to the 2/5 designation in the pyridine nomenclature) or the 5 and 2 positions respectively of a thiophene group respectively; n is 0; and B is —COOH, an alkali metal salt or organic amine salt, or a lower alkyl ester, or —CH<sub>2</sub>OH and the lower alkyl esters and ethers thereof, or —CHO and acetal derivatives thereof.

The most preferred compounds are:

ethyl 6-(2-(4,4-dimethylthiochroman-6-yl)ethynyl)-nicotinate;  
6-(2-(4,4-dimethylthiochroman-6-yl)ethynyl)nicotinic acid;  
6-(2-(4,4-dimethylchroman-6-yl)ethynyl)nicotinic acid;  
ethyl 6-(2-(4,4-dimethylchroman-6-yl)ethynyl)nicotinate;  
ethyl 6-(2-(4,4,7-trimethylthiochroman-6-yl)-ethynyl)-nicotinate;  
ethyl 6-(2-(4,4-dimethyl-1,2,3,4-tetrahydroquinolin-6-yl)ethynyl)nicotinate;  
ethyl 5-(2-(4,4-dimethylthiochroman-6-yl)ethynyl)thiophene-2-carboxylate;  
6-(2-(4,4-dimethylthiochroman-6-yl)-ethynyl)-3-pyridylmethanol; and  
2-(2-(4,4-dimethylthiochroman-6-yl)-ethynyl)-5-pyridinecarboxaldehyde.

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The compounds of this invention may be administered systemically or topically, depending on such considerations as the condition to be treated, need for site-specific treatment, quantity of drug to be administered, and similar considerations.

In the treatment of dermatoses, it will generally be preferred to administer the drug topically, though in certain cases such as treatment of severe cystic acne, oral administration may also be used. Any common topical formulation such as a solution, suspension, gel, ointment, or salve and the like may be used. Preparation of such topical formulations are well described in the art of pharmaceutical formulations as exemplified, for example, *Remington's Pharmaceutical Science*, Edition 17, 10 Mack Publishing Company, Easton, Pa. For topical application, these compounds could also be administered as a powder or spray, particularly in aerosol form.

If the drug is to be administered systemically, it may be confectioned as a powder, pill, tablet or the like, or as a 20 syrup or elixir for oral administration. For intravenous or intraperitoneal administration, the compound will be prepared as a solution or suspension capable of being administered by injection. In certain cases, it may be useful to formulate these compounds in suppository 25 form or as an extended release formulation for deposit under the skin or intermuscular injection.

Other medicaments can be added to such topical formulation for such secondary purposes as treating skin dryness, providing protection against light; other 30 medications for treating dermatoses, preventing infection, reducing irritation, inflammation and the like.

Treatment of dermatoses or any other indications known or discovered to be susceptible to treatment by retinoic acid-like compounds will be effected by administration of the therapeutically effective dose of one or more compounds of the instant invention. A therapeutic concentration will be that concentration which effects reduction of the particular condition, or retards its expansion. In certain instances, the drug potentially could 35 be used in a prophylactic manner to prevent onset of a particular condition. A given therapeutic concentration will vary from condition to condition and in certain instances may vary with the severity of the condition being treated and the patient's susceptibility to treatment. Accordingly, a given therapeutic concentration will be best determined at the time and place through routine experimentation. However, it is anticipated that in the treatment of, for example, acne, or other such dermatoses, that a formulation containing between 40 0.001 and 5 percent by weight, preferably about 0.01 to 1%, will usually constitute a therapeutically effective concentration. If administered systemically, an amount between 0.01 and 100 mg per kg body weight per day, but preferably about 0.1 to 10 mg/kg, will effect a therapeutic result in most instances.

The retinoic acid like activity of these compounds was confirmed through the classic measure of retinoic acid activity involving the effects of retinoic acid on ornithine decarboxylase. The original work on the correlation between retinoic acid and decrease in cell proliferation was done by Verma & Boutwell, *Cancer Research*, 1977, 37, 2196-2201. That reference discloses that ornithine decarboxylase (ODC) activity increased precedent to polyamine biosynthesis. It has been established elsewhere that increases in polyamine synthesis can be correlated or associated with cellular proliferation. Thus, if ODC activity could be inhibited, cell hyperproliferation could be modulated. Although all 45 50 55 60 65

# ATTACHMENT B (cont'd)

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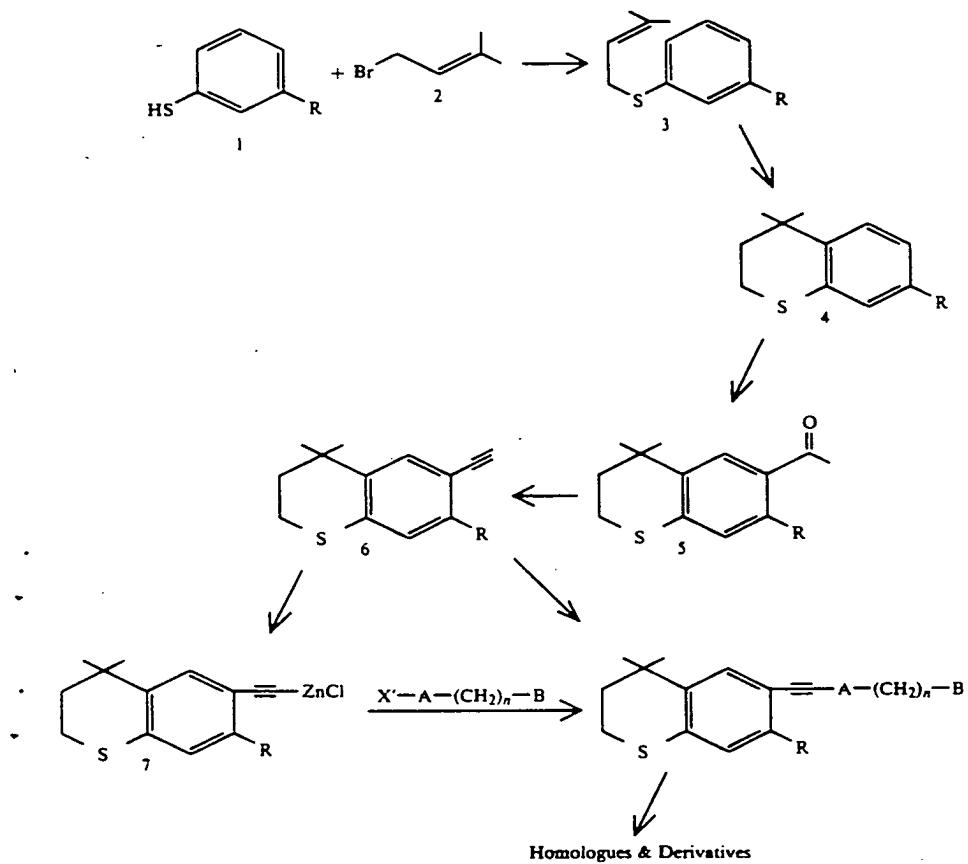
causes for ODC activity increase are unknown, it is known that 12-O-tetradecanoylphorbol-13-acetate (TPA) induces ODC activity. Retinoic acid inhibits this induction of ODC activity by TPA. The compounds of this invention also inhibit TPA induction of ODC as demonstrated by an assay essentially following the procedure set out in *Cancer Res.*: 1662-1670, 1975.

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pounds of formula I when such synthesis is followed in fact and in spirit. The synthetic chemist will readily appreciate that the conditions set out here are specific embodiments which can be generalized to any and all of the compounds represented by formula I.

Compounds of formula I where X is —S— are prepared as per Reaction Scheme I.

Reaction Scheme I



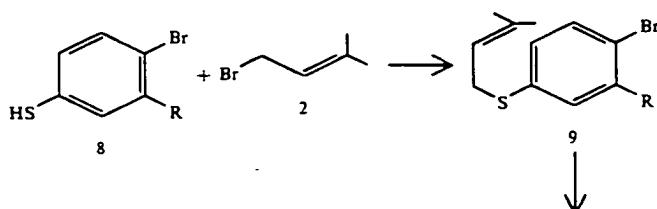
## SPECIFIC EMBODIMENTS

The compounds of this invention can be made by a number of different synthetic chemical pathways. To illustrate this invention, there is here outlined a series of steps which have been proven to provide the com-

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Here, R is hydrogen or a lower alkyl group, A is defined above, n is 0-2 and B is H, or a protected acid, alcohol, aldehyde or ketone. X' is Cl, Br or I when n is 0 but preferably is Br or I when n is 1 or 2.

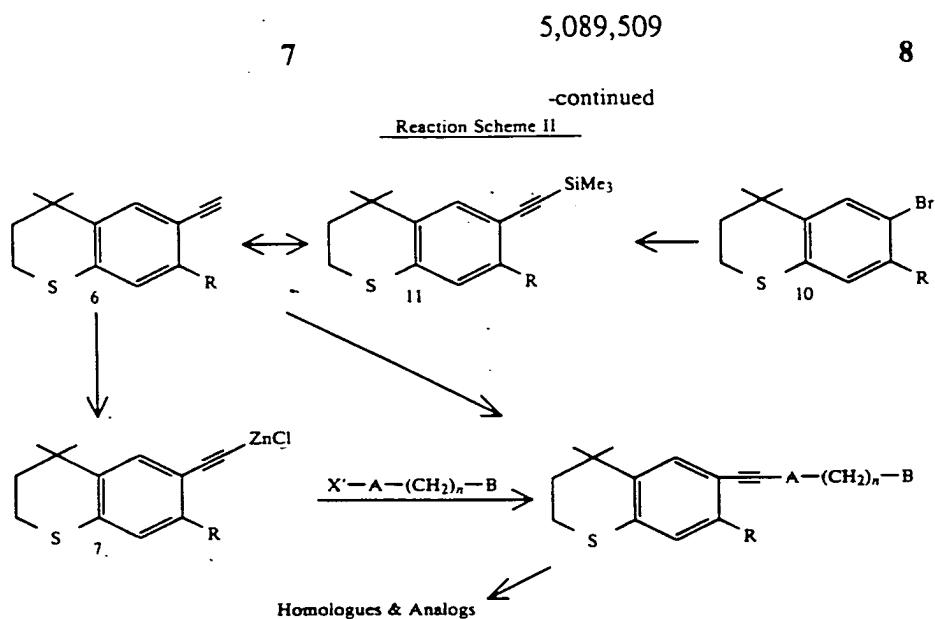
Alternatively, compounds of formula I where X is —S— are prepared as per Reaction Scheme II

Reaction Scheme II



# ATTACHMENT B (cont'd)

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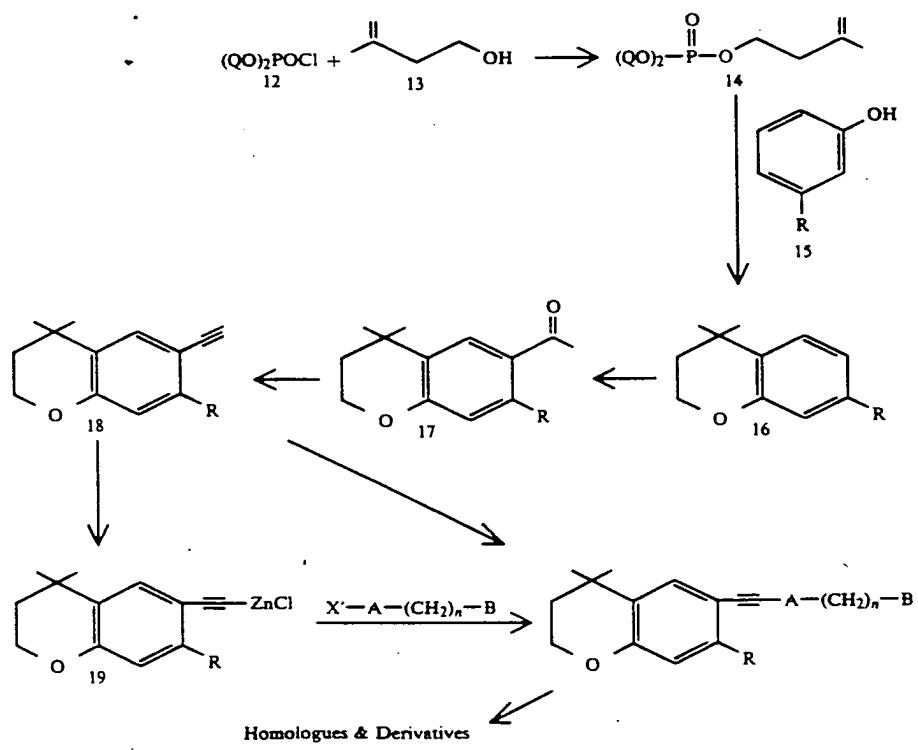
The definitions of R, n, A, B and X' are the same here as in Reaction Scheme I.

Compounds of formula I where X is oxygen are prepared as per Reaction Scheme III.

The definitions of R, n, A, B and X' are the same here as in Scheme I.

Compounds of formula I where X is N—R' where R' is hydrogen or alkyl are prepared as per Reaction Scheme IV.

Reaction Scheme III



# ATTACHMENT B (cont'd)

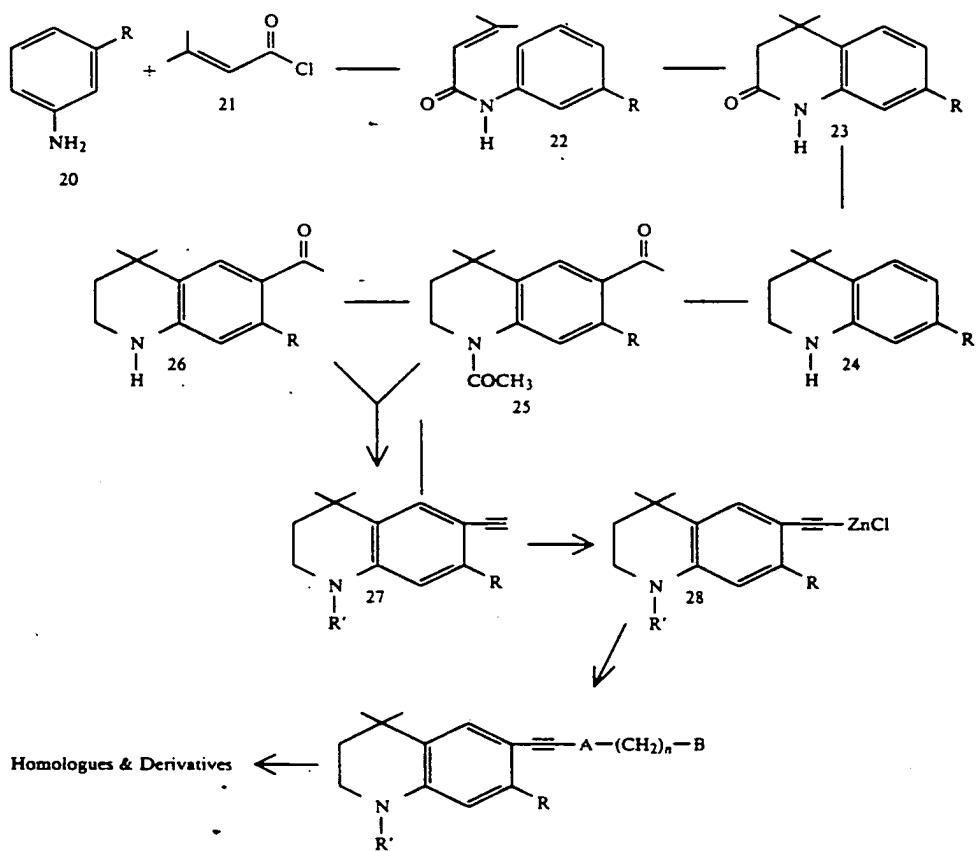
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Reaction Scheme IV

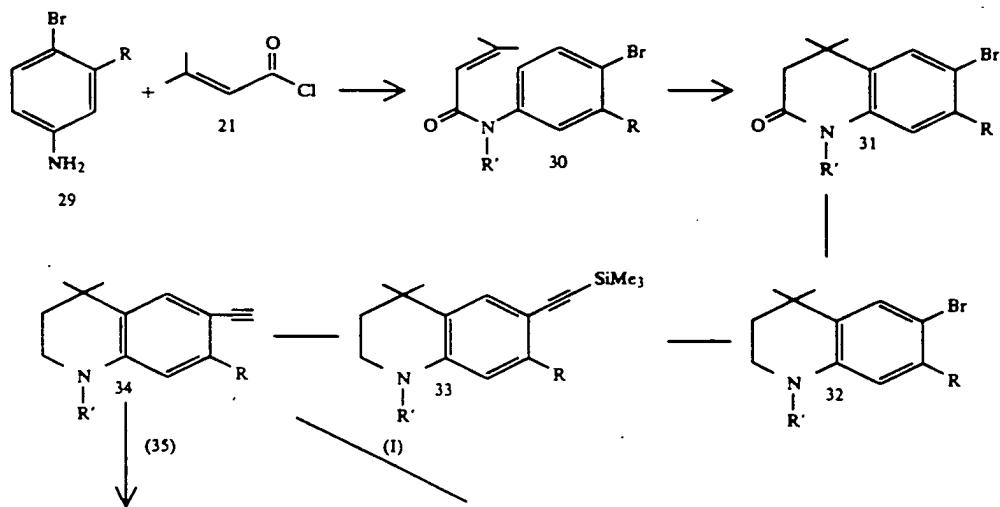


The definitions of R', n, A, B and X' are the same here  
as in Scheme I.

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Alternatively, the sequence of steps outlined in Reaction Scheme V will serve to make such compounds where X is N—R' and R' is H or lower alkyl.

Reaction Scheme V



# ATTACHMENT B (cont'd)

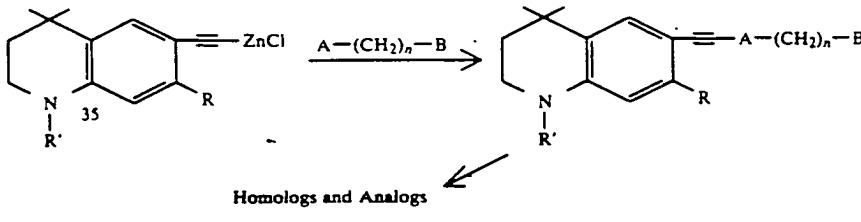
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-continued  
Reaction Scheme V



A general description for making each of the compounds recited in the foregoing Reaction Schemes follows.

In Reaction Scheme I, the following generalized reaction conditions are applicable. The thiophenol of formula 1 is first treated with approximately an equimolar amount of a strong base such as an alkali metal hydroxide, preferably sodium hydroxide, in acetone at reflux. Refluxing is carried out for between 1 and 4 hours, preferably 2.5 hours, after which the solution is treated with an equimolar amount of formula 2, 1-bromo-3-methyl-2-butene (Aldrich), dissolved in acetone. Refluxing is continued for about 2 days after which the solution is stirred for another 24 hours at about room temperature effecting formation of formula 3. It is isolated by conventional means.

Ring closure is effected by treating the sulfide (compound 3), whose formation is described above, with phosphorous pentoxide in the presence of phosphoric acid under an inert atmosphere to give the thiochroman of formula 4. The sulfide is first dissolved in an inert solvent such as benzene, toluene, or the like, and then treated with a small excess of phosphorous pentoxide along with concentrated phosphoric acid. The solution is heated at reflux with stirring under an inert gas such as argon or nitrogen for up to 24 hours. The product is then recovered and purified by conventional means.

The ketone of formula 5 is obtained by treating the thiochroman with acetyl chloride in the presence of aluminum chloride. A suspension of the aluminum chloride in a polar inert solvent is prepared under an inert atmosphere and at reduced temperature, i.e., -10° to 10° C. The inert atmosphere may be argon or nitrogen, preferably argon. The reaction is conveniently carried out in a solvent such as methylene chloride. To the aluminum chloride suspension is added the thiochroman and acetyl chloride via a dropping funnel or similar device. About a 5% molar excess of acetyl chloride and 10% molar excess of aluminum chloride, relative to the thiochroman material, is used. The reaction is effected with agitation (stirring) over 0.5-4 hours at a temperature between 10°-50° C. Preferably the reaction is effected in about 2 hours at room temperature. Then the reaction is quenched with water and/or ice, the product extracted and further purified by distillation or some other appropriate means.

The acetylenic function of formula 6 is introduced by means of lithium diisopropylamide or a similar base at reduced temperature under an inert atmosphere. The reaction is carried out in an ether-type of solvent such as a dialkyl ether or a cyclic ether, for example, tetrahydrofuran, pyran or the like.

More specifically, lithium diisopropylamide is generated in situ by mixing diisopropylamine in a dry solvent such as tetrahydrofuran, which is then cooled, to between -70° and -50° C. under an inert atmosphere.

15 as n-butyl lithium in an appropriate solvent is then added at the reduced temperature and mixed for an appropriate time to permit formation of lithium diisopropylamide (LDA). The ketone of formula 5 (at least a 10% molar excess) is dissolved in the reaction solvent, the solution cooled to that of the LDA mixture, and added to that solution. After brief mixing, the solution is then treated with a dialkyl chlorophosphate, preferably diethyl chlorophosphate in about a 20% molar excess. The reaction solution is then gradually brought to room 25 temperature. This solution is then added to a second lithium diisopropylamide solution which is prepared in situ using dry solvent all under an inert atmosphere, preferably argon, at reduced temperature (e.g. -78° C.). Thereafter, the reaction mixture is again warmed to room temperature where it is stirred for an extended period of time, preferably between 10 and 20 hours, most preferably about 15 hours. The solution is then acidified and the product recovered by conventional means.

35 Formula 7 compounds are prepared under conditions which exclude water and oxygen. A dry, ether-type solvent such as dialkyl ether or a cyclic ether such as a furan or pyran, particularly a tetrahydrofuran, may be used as the solvent. A solution of formula 6 is first prepared under an inert atmosphere such as argon or nitrogen, and then a strong base such as n-butyl lithium is added (in about a 10% molar excess). This reaction is begun at a reduced temperature of between -10° and +10° C., preferably about 0° C. The reaction mixture is stirred for a short period, between 30 minutes and 2 hours, and then treated with about a 10% molar excess of fused zinc chloride dissolved in the reaction solvent. This mixture is stirred for an additional 1-3 hours at about the starting temperature, then the temperature is increased to about ambient temperature for 10-40 minutes.

55 Where a protected heteroaromatic compound is needed to couple with formula 7 compounds, such may be prepared from their corresponding acids, alcohols, ketones or aldehydes. These starting materials, the protected acids, alcohols, aldehydes or ketones, are all available from chemical manufactures or can be prepared by published methods. Acids are esterified by refluxing the acid in a solution of the appropriate alcohol in the presence of thionyl chloride. Refluxing for 2-5 hours provides the desired ester. Alternatively, the acid can be condensed with the appropriate alcohol in the presence of dicyclohexylcarbodiimide and dimethylaminopyridine. The ester is recovered and purified by conventional means. Acetals and ketals are readily made by the method described in March, "Advanced Organic Chemistry," 2nd Edition, McGraw-Hill Book Company, p. 810. Alcohols, aldehydes and ketones all

# ATTACHMENT B (cont'd)

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may be protected by forming respectively, ethers and esters, acetals or ketals by known methods such as those described in McOmie, Plenum Publishing Press, 1973 and *Protecting Groups*, Ed. Greene, John Wiley & Sons, 1981.

To increase the value of n before effecting a coupling reaction, where such compounds are not available from a commercial source, the heteroaromatics where B is —COOH are subjected to homologation by successive treatment under Arndt-Eistert conditions or other homologation procedures. These acids are then esterified by the general procedure outlined in the preceding paragraph. Alternatively, heteroaromatics where B is a different functional may also be homologated by appropriate procedures.

To effect the coupling of the thiochroman moiety with those of formula III, the halo-substituted heteroaromatic compound is dissolved in a dry reaction solvent. The heteroaromatic compound is used in an amount approximating the molar concentration of formula 7. This solution is introduced into a suspension of tetrakis-triphenylphosphine palladium (about a 5 to 10% molar amount relative to the reactants) in the reaction solvent at a temperature of between about —10° and +10° C. This mixture is stirred briefly, for about 15 minutes. To this just prepared mixture is then added the pre-prepared solution of formula 7, the addition being made at about room temperature. This solution is stirred for an extended period, between about 15 and 25 hours at room temperature. The reaction is then quenched with acid and the product separated and purified by conventional means to give the compounds of formula I.

An alternative means for making compounds where n is 1 or 2 is to subject the compounds of formula I where B is an acid or other function to homologation using the Arndt-Eistert method referred to above or other homologation procedures.

The acids and salts derived from formula I are readily obtainable from the corresponding esters. Basic saponification with an alkali metal base will provide the acid. For example, an ester of formula I may be dissolved in a polar solvent such as an alkanol, preferably under an inert atmosphere at room temperature, with about a three molar excess of base, for example, potassium hydroxide. The solution is stirred for an extended period of time, between 15 and 20 hours, cooled, acidified and the hydrolysate recovered by conventional means.

The amide may be formed by any appropriate amidation means known in the art. One way to prepare such compounds is to convert an acid to an acid chloride and then treat that compound with ammonium hydroxide or an appropriate amine. For example, the acid is treated with an alcoholic base solution such as ethanolic KOH (in approximately a 10% molar excess) at room temperature for about 30 minutes. The solvent is removed and the residue taken up in an organic solvent such as diethyl ether, treated with a dialkyl formamide and then a 10-fold excess of oxalyl chloride. This is all effected at a moderately reduced temperature between about —10° and +10° C. The last mentioned solution is then stirred at the reduced temperature for 1–4 hours, preferably 2 hours. Solvent removal provides a residue which is taken up in an inert inorganic solvent such as benzene, cooled to about 0° C. and treated with concentrated ammonium hydroxide. The resulting mixture is stirred at a reduced temperature for 1–4 hours. The product is recovered by conventional means.

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Alcohols are made by converting the corresponding acids to the acid chloride with thionyl chloride or other means (J. March, "Advanced Organic Chemistry", 2nd Edition, McGraw-Hill Book Company), then reducing the acid chloride with sodium borohydride (March, *Ibid*, pg. 1124), which gives the corresponding alcohols. Alternatively, esters may be reduced with lithium aluminum hydride at reduced temperatures. Alkylating these alcohols with appropriate alkyl halides under Williamson reaction conditions (March, *Ibid*, pg. 357) gives the corresponding ethers. These alcohols can be converted to esters by reacting them with appropriate acids in the presence of acid catalysts or dicyclohexylcarbodiimide and dimethylaminopyridine.

Aldehydes can be prepared from the corresponding primary alcohols using mild oxidizing agents such as pyridinium dichromate in methylene chloride (Corey, E. J., Schmidt, G., *Tet. Lett.*, 399, 1979), or dimethyl sulfoxide/oxalyl chloride in methylene chloride (Omura, K., Swern, D., *Tetrahedron*, 1978, 34, 1651).

Ketones can be prepared from an appropriate aldehyde by treating the aldehyde with an alkyl Grignard reagent or similar reagent followed by oxidation.

Acetals or ketals can be prepared from the corresponding aldehyde or ketone by the method described in March, *Ibid*, p 810.

Compounds where B is H are prepared from the corresponding halo-heterocyclic entity preferably where the halogen is I. This haloheterocyclic compound is reacted with the ethynyl entity or the ethynyl zinc chloride entity as represented in Reaction Scheme I and as illustrated in the Examples. Halo-substituted heterocyclic compounds where B is H are commercially available or can be prepared by methods in the literature.

Compounds where X is oxygen are prepared by the steps outlined in Reaction Scheme III. The phosphate of formula 14 is prepared from the corresponding diphenyl chlorophosphate and 3-methyl-3-butene-1-ol available from Aldrich or which may be prepared by means known in the art. It is preferred to prepare formula 14 by dissolving the alcohol of formula 13 in about a 10% excess of pyridine in a polar inert solvent under an inert atmosphere cooled to approximately —10° to 10° C. This solution is then added drop-wise, under an inert atmosphere, to a solution of cooled diphenyl chlorophosphate in about an equal amount of the reaction solvent. About a 2–5% molar excess of diphenyl chlorophosphate relative to the alcohol is employed. The atmosphere may be argon, nitrogen, or another inert gas. The mixture is heated at reflux for between 1 and 5 hours, preferably about 3, to effect the reaction. The product is then recovered by conventional means.

The diphenyl phosphate ester from the preceding paragraph (formula 14) is then reacted with phenol or 3-alkylphenol to effect formation of compound 16. For example, phenol is added to a flask already containing stannic chloride under argon which has been cooled to between —10° to 10° C. After thorough mixing of this combination for about 15 minutes to an hour at the reduced temperature, the phosphate is added at the reduced temperature. Both of these steps are carried out under an inert atmosphere such as argon or nitrogen. When the addition of the phosphate is completed, the mixture is stirred at about ambient temperature for up to 24 hours. Then the reaction is quenched with a dilute solution of aqueous alkali metal base or the like. The

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product is recovered by extraction and other conventional means.

Formula 16 is then acetylated, converted to the acetylene and either the acetylene or the corresponding alkynyl zinc chloride salt coupled with the appropriate heterocycle by the steps outlined in Reaction Scheme I.

The tetrahydroquinoline moiety, that is where X is nitrogen, can be made by the steps outlined in Reaction Scheme IV in part by the method described in European Patent Application 0130795 published Sept. 1, 1985. First, 3-methylcrotonoyl chloride is reacted with aniline to obtain the amide. This amide is then cyclized using aluminum chloride in the absence of solvent. Lithium aluminum hydride or another acceptable reducing agent of similar type is then used to reduce the 2-oxo-1,2,3,4-tetrahydroquinoline, preferably in an inert solvent such as diethyl ether. This amine is then acetylated using acetyl chloride in a polar solvent such as pyridine. This protected amine is then acetylated in the presence of aluminum chloride. The acetyl function on the nitrogen may then be removed by base hydrolysis. Then the acetylated compound is converted to the acetylene and ZnCl salt as outlined in Reaction Scheme I. The acetylene or the salt is then coupled with an appropriate compound of formula III as described before to give compounds of formula I.

Reaction Scheme V sets out an alternative method for making the tetrahydroquinoline compounds illustrated in Reaction Scheme IV.

The following Examples are set out to illustrate the invention, not to limit its scope.

## EXAMPLE 1

### Phenyl-3-methylbut-2-enylsulfide

A mixture of 14.91 g (135.324 mmol) of thiophenol and 5.5 g (137.5 mmol) of NaOH in 100 ml acetone was heated at reflux for 2.5 hours and then treated dropwise with a solution of 20 g (134.19 mmol) of 1-bromo-3-methyl-2-butene in 20 ml acetone. This solution was refluxed for 40 hours and then stirred at room temperature for 24 hours. Solvent was then removed in vacuo, the residue taken up in water, and extracted with 3×50 ml ether. Ether extracts were combined and washed with 3×30 ml of 5% NaOH solution, then water, saturated NaCl solution and dried (MgSO<sub>4</sub>). Solvent was then removed in vacuo and the residue further purified by kugelrohr distillation (80° C., 0.75 mm) to give the title compound as a pale yellow oil.

PMR (CDCl<sub>3</sub>): 81.57 (3H, s), 1.69 (3H, s), 3.52 (2H, d, J~7.7 Hz), 5.29 (1H, t, J~7.7 Hz), 7.14 (1H, t, J~7.0 Hz), 7.24 (2H, t, J~7.0 Hz), 7.32 (2H, d, J~7.0 Hz).

## EXAMPLE 2

### 4,4-Dimethylthiochroman

To a solution of 15.48 g (86.824 mmol) of phenyl-3-methylbut-2-enylsulfide (from Example 1) in 160 ml benzene were added successively 12.6 g (88.767 mmol) of phosphorus pentoxide and 11 ml of 85% phosphoric acid. This solution was refluxed with vigorous stirring under argon for 20 hours, then cooled to room temperature. The supernatant organic layer was decanted and the syrupy residue extracted with 3×50 ml ether. Organic fractions were combined and washed with water, saturated NaHCO<sub>3</sub> and saturated NaCl solution and then dried (MgSO<sub>4</sub>). Solvent was removed in vacuo and the residue purified by kugelrohr distillation (80° C., 0.5 mm) to give the title compound as a pale yellow oil.

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PMR (CDCl<sub>3</sub>): 81.30 (6H, s), 1.90–1.95 (2H, m), 2.95–3.00 (2H, m), 6.96–7.00 (2H, m), 7.04–7.07 (1H, m), 7.30–7.33 (1H, m).

This method can be used to make 7-position alkyl analogues as exemplified by the following compounds: 4,4,7-trimethylthiochroman; 4,4-dimethyl-7-ethylthiochroman; 4,4-dimethyl-7-propylthiochroman; 4,4-dimethyl-7-butylthiochroman; and 10 4,4-dimethyl-7-hexylthiochroman.

## EXAMPLE 3

### 4,4Dimethyl-6-acetylthiochroman

A solution of 14.3 g (80.21 mmol) of 4,4-dimethylthiochroman (from Example 2) and 6.76 g (86.12 mmol) of acetyl chloride in 65 ml benzene was cooled in an ice bath and treated dropwise with 26.712 g (102.54 mmol) of stannic chloride. The mixture was stirred at room temperature for 12 hours, then treated with 65 ml water and 33 ml conc. hydrogen chloride and heated at reflux for 0.5 hours. After being cooled to room temperature, the organic layer was separated and the aqueous layer extracted with 5×50 ml benzene. The recovered organic fractions were combined and washed with 5% sodium carbonate solution, water, saturated NaCl solution and then dried (MgSO<sub>4</sub>). The solvent was removed in vacuo and the residue purified by flash chromatography (silica; 5% ethyl acetate in hexanes) followed by kugelrohr distillation (150° C., 0.7 mm) to give the title compound as a pale yellow oil.

PMR (CDCl<sub>3</sub>): 81.35 (6H, s), 1.92–1.98 (2H, m) 2.54 (3H, s), 3.02–3.08 (2H, m), 7.13 (1H, d, J~8.6 Hz), 7.58 (1H, dd, J~8.6 Hz, 2 Hz), 7.99 (1H, d, J~2 Hz).

This same method may be used to acetylate all compounds made as per Example 2.

## EXAMPLE 4

### 4,4-Dimethyl-6-ethynylthiochroman

To a solution of 1.441 g (14.2405 mmol) of diisopropylamine in 30 ml dry tetrahydrofuran under argon at -78° C. was added dropwise 9 ml of 1.6M (14.4 mmol) n-butyllithium in hexane. After stirring this solution at -78° C. for 1 hour, it was treated dropwise with a solution of 2.95 g (13.389 mmol) of 4,4-dimethyl-6-acetylthiochroman in 5 ml of dry tetrahydrofuran. After another hour of stirring at -78° C., the solution was treated with 2.507 g (14.53 mmol) of diethyl chlorophosphate and brought to room temperature, where it was stirred for 3.75 hours. This solution was then transferred using a double ended needle to a solution of lithium diisopropylamide (prepared as above using 2.882 g (28.481 mmol) of diisopropylamine and 18 ml of 1.6M (28.8 mmol) n-butyllithium in hexane) in 60 ml dry tetrahydrofuran at -78° C. The cooling bath was removed and the solution stirred at room temperature for 15 hours, then quenched with water and acidified to pH 1 with 3N hydrogen chloride. The mixture was stirred at room temperature for 12 hours, then treated with 65 ml water and 33 ml conc. hydrogen chloride and heated at reflux for 0.5 hours. After being cooled to room temperature, the organic layer was separated and the aqueous layer extracted with 5×50 ml benzene. The recovered organic fractions were combined and washed with 5% sodium carbonate solution, water, saturated NaCl solution and then dried (MgSO<sub>4</sub>). The solvent was removed in vacuo and the residue purified by flash chromatography (silica; 5% ethyl acetate in hexanes)

# ATTACHMENT B (cont'd)

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followed by kugelrohr distillation (150° C., 0.7 mm) to give the captioned compound as a pale yellow oil.

PMR ( $\text{CDCl}_3$ ): δ1.35 (6H, s), 1.92–1.98 (2H, m) 2.54 (3H, s), 3.02–3.08 (2H, m), 7.13 (1H, d,  $J$  ~ 8.6 Hz), 7.58 (1H, dd,  $J$  ~ 8.6 Hz, 2 Hz), 7.99 (1H, d,  $J$  ~ 2 Hz).

In the same manner, all acetyl-containing compounds prepared under Example 3 may be converted to their corresponding ethynyl analogues.

**EXAMPLE 5**

**Ethyl 6-chloronicotinate**

A mixture of 15.75 g (0.1 mol) 6-chloronicotinic acid, 6.9 g (0.15 mol) ethanol, 22.7 g (0.11 mol) dicyclohexylcarbodiimide and 3.7 g dimethylaminopyridine in 200 ml methylene chloride was heated at reflux for 2 hours. The mixture was allowed to cool, solvent removed in vacuo and residue subjected to flash chromatography to give the title compound as a low-melting white solid.

PMR ( $\text{CDCl}_3$ ): δ1.44 (3H, t,  $J$  ~ 6.2 Hz) 4.44 (2H, q,  $J$  ~ 4.4 Hz), 7.44 (1H, d,  $J$  ~ 8.1 Hz), 8.27 (1H, dd,  $J$  ~ 8.1 Hz, 3 Hz), 9.02 (1H, d,  $J$  ~ 3 Hz).

This procedure may be used to esterify any of the other halo-substituted acids employed in the making of these compounds such as ethyl 2-(2-chloropyrid-5-yl)acetate; ethyl 5-(2-chloropyrid-5-yl)pentanoate; ethyl 2-(2-iodofur-5-yl)acetate; ethyl 5-(2-iodofur-5-yl)pentanoate; ethyl 2-(2-iodothien-5-yl)acetate; ethyl 5-(2-iodothien-5-yl)pentanoate; ethyl 2-(3-chloropyridazin-6-yl)acetate; ethyl 5-(3-chloropyridazin-6-yl)pentanoate; and the corresponding chloro, or other halo, substituted pyrimidinyl or pyrazinyl analogues of such esters.

**EXAMPLE 6**

**Ethyl**

**6-[2-(4,4-dimethylthiochroman-6-yl)ethynyl]nicotinate**

Reaction vessels used in this procedure were flame dried under vacuum and all operations carried out in an oxygen-free, argon or nitrogen atmosphere. To a solution of 465.7 mg (2.3019 mmol) of 4,4-dimethyl-6-ethynyl-thiochroman in 4 ml of dry tetrahydrofuran at 0° C. was added dropwise 1.5 ml of 1.6M (2.4 mmol) n-butyllithium in hexane. This was stirred at 0° C. for 10 minutes and at room temperature for 10 minutes, cooled again to 0° C. and then treated with a solution of 330 mg (2.4215 mmol) of fused  $\text{ZnCl}_2$  in 4 ml dry tetrahydrofuran using a double ended needle. Thereafter the solution was stirred at 0° C. for 30 minutes, then at room temperature for 10 minutes. A solution of 426.3 mg (2.2967 mmol) of ethyl 6-chloronicotinate (from Example 5) in 4 ml dry tetrahydrofuran was transferred by double ended needle into a suspension of 430 mg (0.37 mmol) of tetrakis(triphenylphosphine) palladium in 4 ml dry tetrahydrofuran and stirred at room temperature for 10 minutes, then treated by double ended needle with the solution of the alkynylzinc prepared above. This mixture was stirred at room temperature for 18 hours, then quenched with 100 ml water. Product was recovered by extraction with 3 × 75 ml ether. Ether fractions were combined and washed with saturated  $\text{NaCl}$  solutions and dried ( $\text{mgSO}_4$ ). Solvent was removed in vacuo and the residue purified by flash chromatography (silica; 5% ethyl acetate in hexane) followed by HPLC (Whatman Partisil M-9 10/50; 4% ethyl acetate in hexane) to give the title compound as a white solid.

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PMR ( $\text{CDCl}_3$ ): δ1.36 (6H, s), 1.45 (3H, t,  $J$  ~ 7 Hz), 1.96–2.00 (2H, m), 3.05–3.09 (2H, m), 4.45 (2H, q,  $J$  ~ 7 Hz), 7.11 (1H, d,  $J$  ~ 8.4 Hz), 7.29 (1H, dd,  $J$  ~ 8.4 Hz, 2.2 Hz), 7.59 (1H, d,  $J$  ~ 7.8 Hz), 7.66 (1H, d,  $J$  ~ 2.2 Hz), 8.30 (1H, dd,  $J$  ~ 7.8 Hz, 2.3 Hz), 9.22 (1H, d,  $J$  ~ 2.3 Hz).

Using this method, but substituting the appropriate ethynylthiochroman from Example 4 and the appropriate halo-substituted heteroaromatic ester from Example 5, the following compounds may be prepared:

- ethyl 6-(2(4,4,7-trimethylthiochroman-6-yl)-ethynyl)nicotinate;
- ethyl 6-(2(4,4-dimethyl-7-ethylthiochroman-6-yl)-ethynyl)nicotinate;
- ethyl 6-(2(4,4-dimethyl-7-propylthiochroman-6-yl)-ethynyl)nicotinate;
- ethyl 6-(2(4,4-dimethyl-7-hexylthiochroman-6-yl)-ethynyl)nicotinate;
- ethyl (2((4,4-dimethylthiochroman-6-yl)ethynyl)pyrid-5-yl)acetate;
- ethyl (2((4,4,7-trimethylthiochroman-6-yl)ethynyl)pyrid-5-yl)acetate;
- ethyl (2((4,4-dimethyl-7-ethylthiochroman-6-yl)-ethynyl)pyrid-5-yl)acetate;
- ethyl (2((4,4-dimethyl-7-hexylthiochroman-6-yl)-ethynyl)pyrid-5-yl)acetate;
- ethyl 3-(2((4,4-dimethylthiochroman-2-yl)ethynyl)pyrid-5-yl)propionate;
- ethyl 3-(2((4,4,7-trimethylthiochroman-6-yl)-ethynyl)pyrid-5-yl)propionate;
- ethyl 3-(2((4,4-dimethyl-7-ethylthiochroman-6-yl)-ethynyl)pyrid-5-yl)propionate;
- ethyl 3-(2((4,4-dimethyl-7-hexylthiochroman-6-yl)-ethynyl)pyrid-5-yl)propionate;
- ethyl 5-(2((4,4-dimethylthiochroman-6-yl)ethynyl)pyrid-5-yl)pentanoate;
- ethyl 5-(2((4,4,7-trimethylthiochroman-6-yl)ethynyl)pyrid-5-yl)pentanoate;
- ethyl 5-(2((4,4-dimethyl-7-ethylthiochroman-6-yl)-ethynyl)pyrid-5-yl)pentanoate;
- ethyl (5((4,4-dimethylthiochroman-6-yl)ethynyl)fur-2-yl)acetate;
- ethyl (5((4,4,7-trimethylthiochroman-6-yl)ethynyl)fur-2-yl)acetate;
- ethyl (5((4,4-dimethyl-7-ethylthiochroman-6-yl)-ethynyl)fur-2-yl)acetate;
- ethyl (5((4,4-dimethyl-7-hexylthiochroman-6-yl)-ethynyl)fur-2-yl)acetate;
- ethyl (5((4,4-dimethylthiochroman-6-yl)ethynyl)fur-2-yl)pentanoate;
- ethyl 5-(5((4,4,7-trimethylthiochroman-6-yl)ethynyl)fur-2-yl)pentanoate;
- ethyl 5-(5((4,4-dimethyl-7-ethylthiochroman-6-yl)-ethynyl)fur-2-yl)pentanoate;
- ethyl 5-(5((4,4-dimethyl-7-hexylthiochroman-6-yl)-ethynyl)fur-2-yl)pentanoate;
- ethyl (5((4,4-dimethylthiochroman-6-yl)ethynyl)thien-2-yl)acetate;
- ethyl (5((4,4,7-trimethylthiochroman-6-yl)ethynyl)thien-2-yl)acetate;
- ethyl (5((4,4-dimethyl-7-ethylthiochroman-6-yl)-ethynyl)thien-2-yl)acetate;
- ethyl (5((4,4-dimethyl-7-hexylthiochroman-6-yl)-ethynyl)thien-2-yl)acetate;
- ethyl 5-(5((4,4-dimethylthiochroman-6-yl)ethynyl)thien-2-yl)pentanoate;
- ethyl 5-(5((4,4,7-trimethylthiochroman-6-yl)ethynyl)thien-2-yl)pentanoate;

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ethyl 5-(5-((4,4-dimethyl-7-ethylthiochroman-6-yl)ethynyl)thien-2-yl)pentanoate;  
 ethyl 5-(5-((4,4-dimethyl-7-hexylthiochroman-6-yl)ethynyl)thien-2-yl)pentanoate;  
 ethyl 6-((4,4-dimethylthiochroman-6-yl)ethynyl)-  
     pyridazin-3-yl)acetate; 5  
 ethyl 6-((4,4,7-trimethylthiochroman-6-yl)ethynyl)-  
     pyridazin-3-yl)acetate;  
 ethyl 6-((4,4-dimethyl-7-ethylthiochroman-6-yl)ethynyl)pyridazin-3-yl)acetate;  
 ethyl 6-((4,4-dimethyl-7-hexylthiochroman-6-yl)ethynyl)pyridazin-3-yl)acetate; 10  
 ethyl 5-(6-((4,4-dimethylthiochroman-6-yl)ethynyl)pyridazin-3-yl)pentanoate;  
 ethyl 5-(6-((4,4,7-trimethylthiochroman-6-yl)ethynyl)pyridazin-3-yl)pentanoate; 15  
 ethyl 5-(6-((4,4-dimethyl-7-ethylthiochroman-6-yl)ethynyl)pyridazin-3-yl)pentanoate;  
 ethyl 5-(6-((4,4-dimethyl-7-hexylthiochroman-6-yl)ethynyl)pyridazin-3-yl)pentanoate; 20  
 ethyl 5-((4,4-dimethylthiochroman-6-yl)ethynyl)pyrimidin-2-yl)acetate;  
 ethyl 5-((4,4,7-trimethylthiochroman-6-yl)ethynyl)pyrimidin-2-yl)acetate; 25  
 ethyl 5-((4,4-dimethyl-7-ethylthiochroman-6-yl)ethynyl)pyrimidin-2-yl)acetate;  
 ethyl 5-((4,4-dimethyl-7-hexylthiochroman-6-yl)ethynyl)pyrimidin-2-yl)acetate; 30  
 ethyl 5-(5-((4,4-dimethylthiochroman-6-yl)ethynyl)pyrimidin-2-yl)pentanoate;  
 ethyl 5-(5-((4,4,7-trimethylthiochroman-6-yl)ethynyl)pyrimidin-2-yl)pentanoate; 35  
 ethyl 5-(5-((4,4-dimethyl-7-ethylthiochroman-6-yl)ethynyl)pyrimidin-2-yl)pentanoate;  
 ethyl 5-(5-((4,4-dimethyl-7-hexylthiochroman-6-yl)ethynyl)pyrimidin-2-yl)pentanoate; 40  
 ethyl 5-((4,4-dimethylthiochroman-6-yl)ethynyl)pyrazin-2-yl)acetate;  
 ethyl 5-((4,4,7-trimethylthiochroman-6-yl)ethynyl)pyrazin-2-yl)acetate;  
 ethyl 5-((4,4-dimethyl-7-ethylthiochroman-6-yl)ethynyl)pyrazin-2-yl)acetate; 45  
 ethyl 5-((4,4-dimethyl-7-hexylthiochroman-6-yl)ethynyl)pyrazin-2-yl)acetate;  
 ethyl 5-((4,4-dimethylthiochroman-6-yl)ethynyl)pyrazin-2-yl)pentanoate;  
 ethyl 5-(5-((4,4,7-trimethylthiochroman-6-yl)ethynyl)pyrazin-2-yl)pentanoate; 50  
 ethyl 5-(5-((4,4-dimethyl-7-ethylthiochroman-6-yl)ethynyl)pyrazin-2-yl)pentanoate; and  
 ethyl 5-(5-((4,4-dimethyl-7-hexylthiochroman-6-yl)ethynyl)pyrazin-2-yl)pentanoate.

*Alternative synthesis:* The title compound of Example 6, ethyl 6-[2-(4,4-dimethylthiochroman-6-yl)ethynyl]nicotinate, was also prepared as follows.

A solution of 15.4 g (76.2 mmol) of 4,4-dimethyl-6-ethylthiochroman and 14.0 g (75.5 mmol) of ethyl-6-chloronicotinate in 35 ml of freshly distilled triethylamine was degassed and then treated under nitrogen with a finely powdered mixture of 1 g (5.25 mmol) of high purity cuprous iodide and 2 g (2.85 mmol) of bis(triphenylphosphine) palladium (II) chloride. The mixture was heated under nitrogen at 55° C. for 20 hours and then cooled to room temperature. The triethylamine was then removed under vacuum and the residue was diluted with 200 ml of a 1:4 mixture of ethyl acetate and hexanes. This mixture was filtered through silica and the filtrate concentrated in vacuo. The resultant residue

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was purified by flash chromatography (silica gel; 15% ethyl acetate in hexanes) and recrystallized from a mixture of ethyl acetate and hexanes to give the title compound as a pale yellow solid.

## EXAMPLE 7

### (3-Methyl-4-bromo-phenyl)-3-methylbut-2-enylsulfide

To a stirred solution of 9.52 g (68 mmol) of 3-methyl-4-bromothiophenol in 80 ml of acetone was added 2.86 g (68 mmol) of powdered sodium hydroxide. This mixture was stirred until the components were dissolved. The reaction mixture was then heated to reflux, and then treated with a solution of 11.26 g (68 mmol) of 4-bromo-2-methyl-2-butene in 20 ml of acetone. The mixture was heated at reflux for a further 0.5 hour, cooled to room temperature and the solvent removed in vacuo. The residue was taken up in 35 ml of water and extracted with ether. The ether extracts were combined and washed successively with water and saturated NaCl solution and then dried ( $MgSO_4$ ). The solvent was removed in vacuo and the residue kugelrohr distilled (140°–145° C., 0.2 mm) to give the title compound as a colorless oil.

PMR ( $CDCl_3$ ): 81.58 (3H, s), 1.70 (3H, s), 2.33 (3H, s), 3.49 (2H, d,  $J$  = 7.8 Hz), 5.26 (1H, t,  $J$  = 7.8 Hz), 6.98 (1H, dd,  $J$  = 8.3 Hz, 2.3 Hz), 7.17 (1H, d  $J$  = 2.3 Hz), 7.38 (1H, d,  $J$  = 8.3 Hz).

## EXAMPLE 8

### 4,4,7-Trimethyl-6-bromothiochroman

To 40 g of a vigorously stirred mixture of 10% phosphorous pentoxide in methanesulfonic acid was added slowly 6.0 g (28.8 mmol) of (3-methyl-4-bromophenyl)-3-methylbut-2-enylsulfide. The mixture was stirred at room temperature for a further 2 hours and was then poured onto ice. The mixture was extracted with  $2 \times 40$  ml of ether and the combined ether extracts were washed successively with water and saturated NaCl solution and then dried. The solvent was removed in vacuo and the residue distilled using a kugelrohr apparatus (130° C.; 0.07 mm) to give the title compound as a viscous oil.

PMR ( $CDCl_3$ ): 81.28 (6H, s) 1.84–1.93 (2H, m), 2.26 (3H, s), 2.95–3.03 (2H, m), 6.94 (1H, s), 7.46 (1H, s).

## EXAMPLE 9

### 4,4,7-Trimethyl-6-trimethylsilylethyneylthiochroman

A mixture of 624 mg (3.0 mmol) of 4,4,7-trimethyl-6-bromothiochroman, 314 mg (3.2 mmol) of trimethylsilylacetylene, 40 mg (0.21 mmol) of cuprous iodide, 80 mg (0.11 mmol) of bis(triphenylphosphine) palladium (II) chloride and 1 ml of triethylamine was degassed under nitrogen and heated in a sealed tube at 85° C. for 15 hours. The mixture was then treated with a further 20 mg (0.11 mmol) of cuprous iodide and 40 mg (0.06 mmol) of the palladium (II) catalyst. The mixture was then heated under a nitrogen atmosphere in the sealed tube at 100° C. for a further 64 hours. The triethylamine was then removed under vacuum and the residue purified by flash chromatography (silica; hexanes) to give the title compound as a yellow oil.

PMR ( $CDCl_3$ ): 80.28 (9H, s), 1.30 (6H, s), 1.88–1.97 (2H, m), 2.33 (3H, s), 2.97–3.05 (2H, m), 6.92 (1H, s), 7.43 (1H, s).

# ATTACHMENT B (cont'd)

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## EXAMPLE 10

### 4,4,7-Trimethyl-6-ethynylthiochroman

A mixture of 380 mg (1.69 mmol) of 4,4,7-trimethyl-6-trimethylsilyl-ethynylthiochroman, 4 ml of isopropanol and 2.5 ml of aqueous 1N potassium hydroxide was degassed under nitrogen and stirred at room temperature for 16 hours. The mixture was concentrated under vacuum and extracted with  $2 \times 10$  ml of ether. The ether extracts were combined and washed successively with water and saturated NaCl solution and then dried ( $\text{MgSO}_4$ ). The solvent was removed in vacuo to give the title compound as a yellow oil.

PMR ( $\text{CDCl}_3$ ): 81.31 (6H, s), 1.88–1.96 (2H, m), 2.35 (3H, s), 3.00–3.08 (2H, m), 3.25 (1H, s), 6.94 (1H, s), 7.47 (1H, s).

## EXAMPLE 11

### Ethyl

### 6-[2-(4,4,7-trimethylthiochroman-6-yl)ethynyl]nicotinate

A mixture of 86 mg (0.4 mmol) of 4,4,7-trimethyl-6-ethynylthiochroman, 85 mg (0.46 mmol) of ethyl 6-chloronicotinate and 0.8 ml of triethylamine was degassed under nitrogen and then treated with a mixture of 10 mg (0.05 mmol) of cuprous iodide and 20 mg (0.03 mmol) of bis(triphenylphosphine) palladium (II) chloride. The reaction mixture was heated at 55° C. under a nitrogen atmosphere for 18 hours. The mixture was then extracted with 1.5 ml of 40% ethyl acetate in hexanes and purified by flash chromatography (silica; 10% ethyl acetate in hexanes) to give the title compound as a yellow solid.

PMR ( $\text{CDCl}_3$ ): 81.32 (6H, s), 1.43 (3H, t,  $J \sim 7.2$  Hz), 2.44 (3H, s), 3.01–3.05 (2H, m), 4.42 (2H, q,  $J \sim 7.2$  Hz), 6.98 (1H, s), 7.54–7.63 (2H, m), 8.27 (1H, dd,  $J \sim 8.3$  Hz, 2.3 Hz), 9.21 (1H, d,  $J \sim 2.3$  Hz).

## EXAMPLE 12

### Ethyl

### 5-(2-(4,4-dimethyl-thiochroman-6-yl)ethynyl)thiophene-2-carboxylate

Using the same general procedure described in the preceding Example 11, but using instead 4,4-dimethyl-6-ethynylthiochroman and ethyl 5-bromo thiophene-2-carboxylate, the title compound was synthesized.

PMR ( $\text{CDCl}_3$ ): 81.31 (6H, s), 1.36 (3H, t,  $J \sim 7.5$  Hz), 1.90–1.94 (2H, m), 2.99–3.03 (2H, m), 4.33 (2H, q,  $J \sim 7.5$  Hz), 7.04 (1H, d,  $J \sim 8.1$  Hz), 7.13–7.18 (2H, m), 7.50 (1H, s), 7.65 (1H, d,  $J \sim 3.9$  Hz).

## EXAMPLE 13

### Ethyl-5-(2-(4,4-dimethylthiochroman-6-yl)ethynyl)-2-furoate

Again using the general procedure of Example 11, but using instead 4,4-dimethyl-6-ethynylthiochroman and ethyl 5-bromo-2-furate, the title compound was synthesized.

PMR ( $\text{CDCl}_3$ ): 81.24 (6H, s), 1.31 (3H, t,  $J \sim 7.0$  Hz), 1.83–1.87 (2H, m), 2.93–2.97 (2H, m), 4.30 (2H, q,  $J \sim 7.0$  Hz), 6.60 (1H, d,  $J \sim 3.4$  Hz), 6.98 (1H, d,  $J \sim 8.1$  Hz), 7.09–7.11 (2H, m), 7.46 (1H, d,  $J \sim 1.7$  Hz).

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## EXAMPLE 14

### Diphenyl-3-methyl-3-but-en-1-yl phosphate

To an ice-cooled solution of 12.2 g (141.65 mmol) of 3-methyl-3-but-en-1-ol (Aldrich) and 11.9 g (150.44 mmol) of pyridine in 100 ml of tetrahydrofuran was added dropwise under argon a solution of 38.5 g (143.21 mmol) of diphenyl chlorophosphate 93 in 100 ml of tetrahydrofuran. The mixture was heated at reflux for 3 hours and then cooled and filtered. The filtrate was concentrated in vacuo and the residue dissolved in 400 ml of 1:1 ether and hexane and then washed with  $2 \times 200$  ml water, 75 ml saturated NaCl solution and dried ( $\text{MgSO}_4$ ). The solvent was removed in vacuo to give the captioned compound as a pale yellow oil.

PMR ( $\text{CDCl}_3$ ): 81.69 (3H, M), 2.37 (2H, t,  $J \sim 7$  Hz), 4.32 (2H, q,  $J \sim 7$  Hz), 4.72 (1H, M), 7.10–7.35 (10H, m).

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## EXAMPLE 15

### 4,4-Dimethylchroman

To a dry, ice-cooled flask containing 34.95 g (0.134 mol) of stannic chloride was added quickly under argon 63.0 g (0.669 mol) of phenol. The mixture was stirred at 0° C. for 0.5 hour and then treated with 43.0 g (0.135 mol) of diphenyl-3-methyl-3-but-en-1-yl phosphate, followed by a 5 ml carbon disulfide rinse. The mixture was stirred at room temperature for 21 hours and then quenched by pouring onto 700 g ice and 1 liter of 1.5N NaOH. The mixture was extracted with  $1 \times 600$  ml and  $2 \times 300$  ml ether. The combined ether fractions were washed with 2N NaOH, saturated NaCl and dried ( $\text{MgSO}_4$ ). Solvent was removed in vacuo and the residue purified by flash chromatography (silica; 2% ether in hexane) to give the title compound as a colorless oil.

PMR ( $\text{CDCl}_3$ ): 81.34 (6H, M), 1.80–1.85 (2H, m), 4.15–4.20 (2H, m), 6.80 (1H, dd,  $J \sim 8.1$  Hz, 1.5 Hz), 6.87 (1H, td,  $J \sim 8.1$  Hz, 1.5 Hz), 7.07 (1H, td,  $J \sim 8.1$  Hz, 1.5 Hz), 7.26 (1H, dd,  $J \sim 8.1$  Hz, 1.5 Hz).

This method also serves to prepare the corresponding 7-alkylchroman compounds, starting with the appropriate 3-alkylphenol, for example:

- 4,4,7-trimethylchroman;
- 4,4-dimethyl-7-ethylchroman;
- 4,4-dimethyl-7-propylchroman;
- 4,4-dimethyl-7-butylchroman;
- 4,4-dimethyl-7-pentylchroman; and
- 4,4-dimethyl-7-hexylchroman.

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## EXAMPLE 16

### 4,4-Dimethyl-6-acetylchroman

To a stirred solution of 7.94 g (48.9425 mmol) of 4,4-dimethylchroman in 70 ml of nitromethane was added under argon 4.0 g (50.96 mmol) of acetyl chloride followed by 6.8 g (51 mmol) of aluminum chloride. This was stirred at room temperature for 5.5 hours and then cooled in an ice bath and treated slowly with 70 ml 6N hydrogen chloride. The resultant mixture was stirred at room temperature for 10 minutes, then treated with 100 ml ether and the organic layer separated. The organic layer was washed with water, saturated  $\text{NaHCO}_3$  and saturated NaCl solutions and dried ( $\text{MgSO}_4$ ). Solvent was removed in vacuo and the residue purified by flash chromatography (silica; 10% ethyl acetate in hexanes). This was followed by kugelrohr distillation (95°–100° C.; 0.15 mm) to give the title compound as a colorless oil.

# ATTACHMENT B (cont'd)

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PMR ( $\text{CDCl}_3$ ): 81.40 (6H, M), 1.95–2.00 (2H, m), 2.58 (3H, M), 4.25–4.30 (2H, m), 6.83 (1H, d,  $J \sim 8.0$  Hz), 7.62 (1H, dd,  $J \sim 8.0$  Hz, 1.5 Hz), 8.00 (1H, d,  $J \sim 1.5$  Hz).

Following the same procedure and using the compounds of Example 15, the following compounds can be prepared:

4,4-dimethyl-6-acetyl-7-methylchroman;  
4,4-dimethyl-6-acetyl-7-ethylchroman;  
4,4-dimethyl-6-acetyl-7-propylchroman;  
4,4-dimethyl-6-acetyl-7-butylchroman;  
4,4-dimethyl-6-acetyl-7-pentylchroman; and  
4,4-dimethyl-6-acetyl-7-hexylchroman.

## EXAMPLE 17

### 4,4-Dimethyl-6-ethynylchroman

To a solution of 2.47 g (24.41 mmol) of diisopropylamine in 40 ml dry tetrahydrofuran under argon at  $-78^\circ\text{C}$ . was added dropwise 15.2 ml of 1.6M (24.32 mmol) n-butyl lithium in hexane. Mixture was stirred at  $-78^\circ\text{C}$ . for 1 hour and then treated dropwise with a solution of 4.98 g (24.38 mmol) of 4,4-dimethyl-6-acetylchroman in 4 ml of dry tetrahydrofuran. After stirring at  $-78^\circ\text{C}$ . for 1 hour, the solution was treated with 4.2 g (24.36 mmol) of diethyl chlorophosphate. The cooling bath was then removed and mixture stirred at room temperature for 2.75 hours. This solution was then transferred using a double ended needle to a solution of lithium diisopropyl amide (prepared as per Example 4) using 4.95 g (48.92 mmol) of diisopropylamine and 30.5 ml of 1.6M (48.8 mmol) n-butyl lithium in hexane in 80 ml dry tetrahydrofuran at  $-78^\circ\text{C}$ . The cooling bath was removed and mixture stirred at room temperature for 18 hours and then quenched with 50 ml water and 25 ml of 3N hydrogen chloride. The mixture was extracted with  $2 \times 100$  ml and  $3 \times 50$  ml of pentane and the combined organic fractions washed with 3N hydrogen chloride, water, saturated  $\text{NaHCO}_3$  and saturated  $\text{NaCl}$  solution and then dried ( $\text{MgSO}_4$ ). Solvent was then removed in vacuo and the residue purified by flash chromatography (silica; 10% ethyl acetate in hexane) followed by kugelrohr distillation ( $70^\circ\text{C}.$ ; 0.35 mm) to give the title compound as a colorless crystalline solid.

PMR ( $\text{CDCl}_3$ ): 81.33 (6H, s), 1.81–1.86 (2H, m), 3.00 (1H, s), 4.19–4.24 (2H, m), 6.75 (1H, d,  $J \sim 8.5$  Hz), 7.22 (1H, dd,  $J \sim 8.5$  Hz, 2.3 Hz), 7.44 (1H, d,  $J \sim 2.3$  Hz).

This procedure serves to convert all acetyl-containing compounds prepared as per Example 16 to their corresponding ethynyl-containing compounds.

## EXAMPLE 18

### Ethyl

#### 6-[2-(4,4-dimethylchroman-6-yl)ethynyl]nicotinate

Reaction vessels used in this procedure were flame dried under vacuum and all operations were carried out in an oxygen-free, argon or nitrogen atmosphere. To a solution of 509.4 mg (2.74 mmol) of 4,4-dimethyl-6-ethynylchroman in 4 ml of dry tetrahydrofuran at  $0^\circ\text{C}$ . was added dropwise 1.72 ml of 1.6M (2.75 mmol) of n-butyl lithium in hexane. Stirring was commenced at  $0^\circ\text{C}$ . for 30 minutes and at room temperature for 15 minutes, after which the solution was cooled again to  $0^\circ\text{C}$ . and then treated with a solution of 380 mg (2.79 mmol) of fused zinc chloride in 5 ml of dry tetrahydrofuran using a double ended needle. The resulting solution was stirred at  $0^\circ\text{C}$ . for 1 hour and then at room temperature for 15 minutes. A solution of 628.6 mg (2.74 mmol) of ethyl 6-chloronicotinate in 4 ml of dry tetrahydrofuran was transferred by double ended needle into a suspen-

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sion of 380 mg (0.33 mmol) of tetrakis(triphenylphosphine palladium in 5 ml dry tetrahydrofuran and mixture stirred at room temperature for 15 minutes and then treated by double ended needle with the solution of alkynylzinc prepared above. The mixture was stirred at room temperature for 20 hours and then quenched with ice and 30 ml of 3N hydrogen chloride. The mixture was extracted with  $3 \times 75$  ml ether and ether extracts were combined and washed successively with saturated  $\text{NaHCO}_3$  and saturated  $\text{NaCl}$  and then dried ( $\text{MgSO}_4$ ). Solvent was removed in vacuo and the residue further purified by flash chromatography (silica; 10% ethyl acetate in hexane) to give the title compound as a yellow solid.

PMR ( $\text{CDCl}_3$ ): 81.36 (6H, s), 1.44 (3H, t,  $J \sim 7.1$  Hz), 1.83–1.87 (2H, m), 4.22–4.26 (2H, m), 4.44 (2H, q,  $J \sim 7.1$  Hz), 6.80 (1H, d,  $J \sim 7.6$  Hz), 7.35 (1H, d,  $J \sim 8.9$  Hz), 7.58 (1H, d,  $J \sim 7.6$  Hz), 7.60 (1H, M), 8.28 (1H, d,  $J \sim 8.9$  Hz), 9.21 (1H, s).

By this method, using the appropriate precursors, the following compounds are prepared:

ethyl 6-(2-(4,4,7-trimethylchroman-6-yl)-ethynyl)nicotinate;  
ethyl 6-(2-(4,4-dimethyl-7-ethylchroman-6-yl)-ethynyl)nicotinate;  
ethyl 6-(2-(4,4-dimethyl-7-propylchroman-6-yl)-ethynyl)nicotinate;  
ethyl 6-(2-(4,4-dimethyl-7-hexylchroman-6-yl)-ethynyl)nicotinate;  
ethyl (2-((4,4-dimethylchroman-6-yl)ethynyl)pyrid-5-yl)acetate;  
ethyl (2-((4,4,7-trimethylchroman-6-yl)ethynyl)pyrid-5-yl)acetate;  
ethyl (2-((4,4-dimethyl-7-ethylchroman-6-yl)ethynyl)pyrid-5-yl)acetate;  
ethyl (2-((4,4-dimethyl-7-hexylchroman-6-yl)ethynyl)pyrid-5-yl)acetate;  
ethyl 3-(2-((4,4-dimethylchroman-2-yl)ethynyl)pyrid-5-yl)propionate;  
ethyl 3-(2-((4,4,7-trimethylchroman-6-yl)ethynyl)pyrid-5-yl)propionate;  
ethyl 3-(2-((4,4-dimethyl-7-ethylchroman-6-yl)ethynyl)pyrid-5-yl)propionate;  
ethyl 3-(2-((4,4-dimethyl-7-hexylchroman-6-yl)ethynyl)pyrid-5-yl)propionate;  
ethyl 5-(2-((4,4-dimethylchroman-6-yl)ethynyl)pyrid-5-yl)pentanoate;  
ethyl 5-(2-((4,4,7-trimethylchroman-6-yl)ethynyl)pyrid-5-yl)pentanoate;  
ethyl 5-(2-((4,4-dimethyl-7-ethylchroman-6-yl)ethynyl)pyrid-5-yl)pentanoate;  
ethyl 5-(2-((4,4-dimethyl-7-hexylchroman-6-yl)ethynyl)pyrid-5-yl)pentanoate;  
ethyl 5-(2-((4,4-dimethylchroman-2-yl)ethynyl)pyrid-5-yl)propionate;  
ethyl 5-(2-((4,4,7-trimethylchroman-6-yl)ethynyl)pyrid-5-yl)propionate;  
ethyl 5-(2-((4,4-dimethyl-7-ethylchroman-6-yl)ethynyl)pyrid-5-yl)propionate;  
ethyl 5-(2-((4,4-dimethyl-7-hexylchroman-6-yl)ethynyl)pyrid-5-yl)propionate;  
ethyl 5-(5-((4,4-dimethylchroman-6-yl)ethynyl)fur-2-yl)pentanoate;  
ethyl 5-(5-((4,4,7-trimethylchroman-6-yl)ethynyl)fur-2-yl)pentanoate;  
ethyl 5-(5-((4,4-dimethyl-7-ethylchroman-6-yl)ethynyl)fur-2-yl)pentanoate;  
ethyl 5-(5-((4,4-dimethyl-7-hexylchroman-6-yl)ethynyl)fur-2-yl)pentanoate;  
ethyl 5-(5-((4,4-dimethylchroman-2-yl)ethynyl)fur-2-yl)pentanoate;  
ethyl 5-(5-((4,4,7-trimethylchroman-6-yl)ethynyl)fur-2-yl)pentanoate;  
ethyl 5-(5-((4,4-dimethyl-7-ethylchroman-6-yl)ethynyl)fur-2-yl)pentanoate;

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ethyl 5-(5-((4,4-dimethyl-7-hexylchroman-6-yl)-ethynyl)furan-2-yl)pentanoate;  
 ethyl (5-((4,4-dimethylchroman-6-yl)ethynyl)thien-2-yl)acetate;  
 ethyl (5-((4,4,7-trimethylchroman-6-yl)ethynyl)thien-2-yl)acetate; 5  
 ethyl (5-((4,4-dimethyl-7-ethylchroman-6-yl)ethynyl)-thien-2-yl)acetate;  
 ethyl (5-((4,4-dimethyl-7-hexylchroman-6-yl)ethynyl)-thien-2-yl)acetate; 10  
 ethyl 5-(5-((4,4-dimethylchroman-6-yl)ethynyl)thien-2-yl)pentanoate;  
 ethyl 5-5-((4,4,7-trimethylchroman-6-yl)-ethynyl)thien-2-yl)pentanoate;  
 ethyl 5-(5-((4,4-dimethyl-7-ethylchroman-6-yl)ethynyl)-thien-2-yl)pentanoate; 15  
 ethyl 5-(5-((4,4-dimethyl-7-hexylchroman-6-yl)ethynyl)thien-2-yl)pentanoate;  
 ethyl 5-(5-((4,4-dimethylchroman-6-yl)ethynyl)pyridazin-3-yl)acetate; 20  
 ethyl (6-((4,4,7-trimethylchroman-6-yl)ethynyl)pyridazin-3-yl)acetate;  
 ethyl (6-((4,4-dimethyl-7-ethylchroman-6-yl)ethynyl)-pyridazin-3-yl)acetate;  
 ethyl (6-((4,4-dimethyl-7-hexylchroman-6-yl)ethynyl)pyridazin-3-yl)acetate; 25  
 ethyl 5-(6-((4,4-dimethylchroman-6-yl)ethynyl)pyridazin-3-yl)pentanoate;  
 ethyl 5-(6-((4,4,7-trimethylchroman-6-yl)-ethynyl)-pyridazin-3-yl)pentanoate; 30  
 ethyl 5-(6-((4,4-dimethyl-7-ethylchroman-6-yl)ethynyl)-pyridazin-3-yl)pentanoate;  
 ethyl 5-(6-((4,4-dimethyl-7-hexylchroman-6-yl)ethynyl)-pyridazin-3-yl)pentanoate;  
 ethyl 5-(6-((4,4-dimethyl-7-ethylchroman-6-yl)ethynyl)-pyridazin-3-yl)pentanoate; 35  
 ethyl 5-(6-((4,4-dimethyl-7-hexylchroman-6-yl)ethynyl)pyridazin-3-yl)pentanoate;  
 ethyl (5-((4,4-dimethylchroman-6-yl)ethynyl)pyrimidin-2-yl)acetate;  
 ethyl (5-((4,4,7-trimethylchroman-6-yl)ethynyl)pyrimidin-2-yl)acetate; 40  
 ethyl (5-((4,4-dimethyl-7-ethylchroman-6-yl)ethynyl)-pyrimidin-2-yl)acetate;  
 ethyl (5-((4,4-dimethyl-7-hexylchroman-6-yl)ethynyl)-pyrimidin-2-yl)acetate;  
 ethyl 5-(5-((4,4-dimethylchroman-6-yl)ethynyl)pyrimidin-2-yl)pentanoate; 45  
 ethyl 5-(5-((4,4,7-trimethylchroman-6-yl)-ethynyl)-pyrimidin-2-yl)pentanoate;  
 ethyl 5-(5-((4,4-dimethyl-7-ethylchroman-6-yl)ethynyl)-pyrimidin-2-yl)pentanoate; 50  
 ethyl 5-(5-((4,4-dimethyl-7-hexylchroman-6-yl)ethynyl)pyrimidin-2-yl)pentanoate;  
 ethyl (5-((4,4-dimethylchroman-6-yl)ethynyl)pyrazin-2-yl)acetate; 55  
 ethyl (5-((4,4,7-trimethylchroman-6-yl)ethynyl)pyrazin-2-yl)acetate;  
 ethyl (5-((4,4-dimethyl-7-ethylchroman-6-yl)ethynyl)-pyrazin-2-yl)acetate;  
 ethyl (5-((4,4-dimethyl-7-hexylchroman-6-yl)ethynyl)-pyrazin-2-yl)acetate; 60  
 ethyl 5-(5-((4,4-dimethylchroman-6-yl)ethynyl)pyrazin-2-yl)pentanoate;  
 ethyl 5-(5-((4,4,7-trimethylchroman-6-yl)-ethynyl)pyrazin-2-yl)pentanoate;  
 ethyl 5-(5-((4,4-dimethyl-7-ethylchroman-6-yl)ethynyl)-pyrazin-2-yl)pentanoate; 65  
 ethyl 5-(5-((4,4-dimethyl-7-hexylchroman-6-yl)ethynyl)pyrazin-2-yl)pentanoate; and  
 ethyl 5-(5-((4,4-dimethyl-7-hexylchroman-6-yl)ethynyl)pyrazin-2-yl)pentanoate.

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EXAMPLE 19.

*N*-(4-Bromophenyl)-3,3-dimethylacrylamide

To a solution of 9.48 g (80 mmol) of 3,3-dimethylacryloyl chloride in 200 ml of dry tetrahydrofuran (THF) was added with vigorous shaking a solution of 13.76 g (80 mmol) of 4-bromoaniline in 300 ml of dry THF. The mixture stood at room temperature for 2 hours and was then treated with 80 g of ice followed by 200 ml of hexane. The organic layer was separated and the aqueous layer was extracted with 2 × 50 ml of hexanes. The organic layers were combined and washed successively with 30 ml of water and 2 × 30 ml of saturated NaCl solution and then dried (MgSO<sub>4</sub>). The solvent was removed in vacuo and the residue purified by recrystallization from an ethyl acetate and hexanes mixture to give the title compound as colorless crystals.

PMR (CDCl<sub>3</sub>): δ1.91 (3H, s), 2.23 (3H, s), 5.73 (1H, broad s), 7.38–7.55 (5H, m).

EXAMPLE 20

4,4-Dimethyl-6-bromo-2-oxo-1,2,3,4-tetrahydroquinoline

To 6.7 g (26.02 mmol) of molten *N*-(4-bromophenyl)-3,3-dimethylacrylamide (heated to 135° C.) was added 4.15 g (31.09) of aluminum chloride over 25 minutes. The reaction mixture was stirred at 130° C. for 16 hours and then treated with a further 1 g of aluminum chloride. The reaction mixture was heated at 130° C. for a further 9 hours and then cooled to room temperature. The reaction was then quenched by the slow addition of 100 ml of ice cold water with slight warming of flask to facilitate mixing. The mixture was extracted with 1 × 100 ml and 4 × 50 ml of ether. The organic extracts were combined and washed with 25 ml of saturated NaCl solution and then dried (MgSO<sub>4</sub>). The solvent was removed in vacuo and the residue purified by flash chromatography (silica; 30% ethyl acetate in hexanes) to give the title compound as a pale yellow solid.

PMR (CDCl<sub>3</sub>): δ1.37 (6H, s), 2.53 (2H, s), 6.85 (1H, d, J~8.4 Hz), 7.32 (1H, dd, J~8.4 Hz, 2.1 Hz), 7.43 (1H, d, J~2.1 Hz), 10.12 (1H, broad s).

EXAMPLE 21

4,4-Dimethyl-6-bromo-1,2,3,4-tetrahydroquinoline

To 23.5 ml of 1.0M (23.5 mmol) lithium aluminum hydride in THF, heated to reflux under nitrogen, was added a solution of 4.95 g (19.48 mmol) of 4,4-dimethyl-6-bromo-2-oxo-1,2,3,4-tetrahydroquinoline in 50 ml of dry THF and 100 ml of dry diethyl ether via a double-ended needle. The mixture was heated at a reflux for 2 hours and then cooled to room temperature. The reaction mixture was then quenched by the slow addition of 25 ml of water followed by 50 ml of 5% NaOH solution. The mixture was extracted with 2 × 25 ml of ether, the organic extracts were combined and washed successively with 25 ml each of water and saturated NaCl solution and then dried (MgSO<sub>4</sub>). The solvent was removed in vacuo and the residue purified by flash chromatography (silica; 15% ethyl acetate in hexanes) to give the title compound as a brown oil.

PMR (CDCl<sub>3</sub>): δ1.27 (6H, s), 1.67–1.74 (2H, m), 3.23–3.32 (2H, m), 3.90 (1H, broad s), 6.33 (1H, d, J~8.4 Hz), 7.10 (1H, dd, J~8.4 Hz, 2.3 Hz), 7.25 (1H, d, J~2.3 Hz).

# ATTACHMENT B (cont'd)

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## EXAMPLE 22

### 4,4-Dimethyl-6-trimethylsilylethylynol-1,2,3,4-tetrahydroquinoline

A solution of 1.608 g (6.7 mmol) of 4,4-dimethyl-6-bromo-1,2,3,4-tetrahydroquinoline in 1.5 ml of triethylamine in a heavy-walled tube was degassed under argon and then treated with 75 mg (0.39 mmol) of cuprous iodide and 150 mg (0.21 mmol) of bis(triphenylphosphine) palladium (II) chloride. The mixture was degassed again under argon, treated with 2.09 g (21.2 mmol) of trimethylsilylacetylene and the tube was sealed. The mixture was heated at 50° C. for 48 hours. After cooling to room temperature methylene chloride was added to the reaction mixture and the mixture filtered. The filtrate was concentrated in vacuo and the residue purified by flash chromatography (silica; 10% ethyl acetate in hexanes) to give the title compound as a yellow oil.

PMR ( $\text{CDCl}_3$ ): 80.20 (9H, s), 1.20 (6H, s), 1.57–1.63 (2H, m), 3.16–3.25 (2H, m), 4.02 (1H, broad s), 6.24 (1H, d,  $J$  ~ 8.2 Hz), 7.00 (1H, dd,  $J$  ~ 8.2 Hz, 1.8 Hz), 7.26 (1H, d,  $J$  ~ 1.8 Hz).

## EXAMPLE 23

### 4,4-Dimethyl-6-ethynol-1,2,3,4-tetrahydroquinoline

To a solution of 569 mg (2.21 mmol) of 4,4-dimethyl-6-trimethylsilylethylynol-1,2,3,4-tetrahydroquinoline in 3 ml of isopropanol was added, under argon, 1 ml of 1N aqueous KOH solution. The reaction mixture was stirred at room temperature for 36 hours and the isopropanol was removed under vacuum. The residue was extracted with ether and the ether extract was washed successively with water and saturated NaCl solution and then dried ( $\text{MgSO}_4$ ). The solvent was removed in vacuo and the residue was purified by flash chromatography (silica; 10% ethyl acetate in hexanes) to give the title compound as a brown oil.

PMR ( $\text{CDCl}_3$ ): 81.26 (6H, s), 1.65–1.72 (2H, m), 2.96 (1H, s), 3.27–3.34 (2H, m), 6.34 (1H, d,  $J$  ~ 8.3 Hz), 7.08 (1H, dd,  $J$  ~ 8.3 Hz, 1.6 Hz), 7.33 (1H, d,  $J$  ~ 1.6 Hz).

## EXAMPLE 24

### 6-(2-(4,4-dimethylthiocroman-6-yl)ethynyl)nicotinic acid

The absolute ethanol used in this experiment was degassed by applying a vacuum while simultaneously bubbling nitrogen through it. A solution of 101.1 mg (0.30 mmol) of ethyl 6-(2-(4,4-dimethylthiocroman-6-yl)ethynyl)-nicotinate in 2 ml ethanol was treated under argon with 0.7 ml of a 1.81M (1.27 mmol) solution of potassium hydroxide in ethanol and water. This mixture was stirred at room temperature for 60 hours and then solvent removed in vacuo. The residue was dissolved in 25 ml of water and extracted with 25 ml of ether. The aqueous layer was acidified with glacial acetic acid and extracted with 4 × 50 ml of ether. Ether extracts were combined and washed with water, then saturated NaCl and dried ( $\text{MgSO}_4$ ). Solvent was then removed in vacuo to give the title compound. PMR ( $(\text{CD}_3)_2\text{CO}$ ): 81.40 (6H, s) 1.88–1.92 (2H, m), 4.26–4.30 (2H, m), 6.82 (1H, d,  $J$  ~ 8.7 Hz), 7.37 (1H, dd,  $J$  ~ 7.6 Hz, 2.2 Hz), 7.62 (1H, M), 7.63 (1H, d,  $J$  ~ 8.7 Hz), 8.37 (1H, dd,  $J$  ~ 7.6 Hz, 2.2 Hz), 9.27 (1H, d,  $J$  ~ 2.2 Hz).

Proceeding in the same manner 6-(2-(4,4-dimethylthiocroman-6-yl)ethynyl)nicotinic acid was prepared

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from ethyl 6-(2-(4,4-dimethylthiocroman-6-yl)ethynyl)nicotinate.

PMR ( $\text{CDCl}_3(\text{CD}_3)_2\text{CO}$ ): 81.37 (6H, M), 1.99 (2H, m), 3.09 (2H, m), 7.10 (1H, d,  $J$  ~ 8.1 Hz), 7.28 (1H, dd,  $J$  ~ 8.1 Hz), 2.1 Hz), 7.64 (1H, dd,  $J$  ~ 7.8 Hz), 1.8 Hz), 7.65 (1H, d,  $J$  ~ 7.8 Hz, 1.5 Hz), 9.24 (1H, m).

Proceeding in the same manner, the esters prepared as per the preceding Examples may be converted to their corresponding acid.

## EXAMPLE 25

### 6-(2-(4,4-Dimethyl-thiocroman-6-yl)-ethynyl)-3-pyridylmethanol

To 3.0 ml of 1M lithium aluminum hydride (3.0 mmol) in THF, cooled to –78° C., was added dropwise over 5 min a solution of 2.0 g (5.9 mmol) of ethyl 6-(2-(4,4-dimethylthiocroman-6-yl)-ethynyl)nicotinate in 5 ml of THF. The reaction mixture was stirred at –78° C. for 40 min and then treated with 2 ml of water. The mixture was warmed to room temperature and the organic layer was separated. The aqueous layer was extracted with 3 × 10 ml of ether. The organic extracts were combined and washed successively with 1 × 10 ml of dilute HCl, 3 × 10 ml of water and 1 × 15 ml of saturated NaCl solution and then dried ( $\text{MgSO}_4$ ). The solvent was removed in vacuo and the residue purified by flash chromatography (silica; 50% ethyl acetate in hexanes) to give the title compound as a pale yellow solid.

PMR ( $\text{CDCl}_3$ ): 81.33 (6H, s), 1.91–1.98 (2H, m), 3.01–3.07 (2H, m), 4.75 (2H, s), 7.08 (1H, d,  $J$  ~ 8.2 Hz), 7.23 (1H, dd,  $J$  ~ 8.2 Hz, 1.7 Hz), 7.46 (1H, d,  $J$  ~ 7.9 Hz), 7.60 (1H, d,  $J$  ~ 1.2 Hz), 7.71 (1H, dd,  $J$  ~ 7.9 Hz, 1.2 Hz), 8.51 (1H, broad s).

## EXAMPLE 26

### 2-(4,4-dimethyl-thiocroman-6-yl)ethynyl)-5-bromopyridine

A mixture of 6.36 g (31.5 mmol) of 4,4-dimethyl-6-ethynylthiocroman, 7.46 g (31.5 mmol) of 2,5-dibromopyridine, 122 mg (0.64 mmol) of cuprous iodide, 224 mg (0.32 mmol) of bis(triphenylphosphine) palladium (II) chloride and 70 ml of freshly distilled triethylamine was degassed under nitrogen and stirred at room temperature for 1 hour. The mixture was then treated with 180 ml of ether and 40 ml of water and the organic layer was separated. The aqueous layer was extracted with ether, the organic layers were combined and then washed with 2 × 40 ml of water, 2 × 40 ml of saturated NaCl solution and then dried ( $\text{K}_2\text{CO}_3$ ). The solvent was removed in vacuo and the residue purified by flash chromatography (silica; 5% ethyl acetate in hexanes) and recrystallization from ethyl acetate and hexane to give the title compound as a pale brown solid.

PMR ( $\text{CDCl}_3$ ): 81.34 (6H, s), 1.94–1.98 (2H, m), 3.04–3.08 (2H, m), 7.08 (1H, d,  $J$  ~ 8.4 Hz), 7.23 (1H, dd,  $J$  ~ 8.4 Hz, 1.8 Hz), 7.38 (1H,  $J$  ~ 8.4 Hz), 7.60 (1H, d,  $J$  ~ 1.8 Hz), 7.78 (1H, dd,  $J$  ~ 8.4, 2.3 Hz), 8.66 (1H, d,  $J$  ~ 2.3 Hz).

## EXAMPLE 27

### 2-(2-(4,4-dimethylthiocroman-6-yl)-ethynyl)-5-pyridinecarboxaldehyde

To a cooled (–78° C.) solution of 358 mg (1.0 mmol) of 2-(4,4-dimethylthiocroman-6-yl)ethynyl-5-bromopyridine in 5 ml of anhydrous ether was added slowly under nitrogen 1.3 ml of 1.7M (2.21 mmol) tert-

# ATTACHMENT B (cont'd)

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butyl lithium in pentane. The mixture was stirred at -78° C. for 1 h and then treated with 95 mg (1.3 mmol) of anhydrous dimethylformamide. The mixture was stirred at -78° C. for a further 0.5 hours, then warmed to 0° C. and treated with 5 ml of saturated NH<sub>4</sub>Cl solution followed by 5 ml of ether. The organic layer was separated and the aqueous layer was extracted with ether. The organic layers were combined, washed successively with water and saturated NaCl solution and then dried (MgSO<sub>4</sub>). The solvent was then removed in vacuo and the residue purified by flash chromatography (silica; 15% ethyl acetate in hexanes) followed by high pressure liquid chromatography (Whatman M-9 Partisil 10/50 column, 15% ethyl acetate in hexanes) to give the title compound as a pale yellow solid.

PMR (CDCl<sub>3</sub>): δ 1.33 (6H, s), 1.93–1.97 (2H, m), 3.03–3.07 (2H, m), 7.08 (1H, d, J = 8.2 Hz), 7.26 (1H, dd, J = 8.2 Hz, 1.8 Hz), 7.63–7.65 (2H, m), 8.14 (2H, dd, J = 8.0 Hz, 2.3 Hz) 9.05 (1H, d, J = 2.3 Hz), 10.1 (1H, s).

## EXAMPLE 28

### 2-[2-(4,4-Dimethylchroman-6-yl)ethynyl]-5-hydroxymethylpyridine

A 250 ml 3-necked flask is fitted with a stirrer, a dropping funnel, a nitrogen inlet and a thermometer. In the flask is placed a solution of 379.5 mg (10 mmol) of lithium aluminum hydride in 30 ml of dry diethyl ether. The solution is cooled to -65° C. under nitrogen and a solution of 3.2343 g (10 mmol) of ethyl 6-[2-(4,4-dimethylchroman-6-yl)ethynyl]nicotinate in 15 ml of dry ether is added dropwise at a rate such that the temperature does not exceed -60° C. The mixture is stirred at -30° C. for 1 hour and the excess hydride is then destroyed by the addition of 300 mg (3.4 mmol) of ethyl acetate. The reaction mixture is then hydrolyzed by adding 3 ml of saturated ammonium chloride solution and allowing the temperature to rise to room temperature. The mixture is then filtered and the residue washed with ether. The ether layer is then washed with saturated sodium chloride solution, dried (MgSO<sub>4</sub>) and then concentrated in vacuo. The residue is purified by chromatography followed by recrystallization to give the title compound.

By the same process, acids or esters of this invention may be converted to their corresponding primary alcohol.

## EXAMPLE 29

### 2-[2-(4,4-Dimethylchroman-6-yl)ethynyl]-5-acetoxymethylpyridine

A solution of 2.81 g (10 mmol) of 2-[2-(4,4-dimethylchroman-6-yl)ethynyl]-5-hydromethylpyridine, 600 mg (10 mmol) of glacial acetic acid, 2.06 g (10 mmol) of dicyclohexylcarbodiimide and 460 mg (3.765 mmol) of 4-dimethylaminopyridine in 150 ml methylene chloride is stirred at room temperature for 48 hours. The reaction mixture is then filtered and the residue washed with 50 ml of methylene chloride. The filtrate is then concentrated in vacuo and the residue is purified by chromatography followed by recrystallization to give the title compound.

Proceeding in the same manner, other alcohols of this invention may be esterified.

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## EXAMPLE 30

### 2-(2-(4,4-Dimethylchroman-6-yl)ethynyl)pyridine-5-carboxaldehyde

A solution of 1.396 g (11 mmol) of freshly distilled oxalyl chloride in 25 ml of methylene chloride is placed in a 4-necked flask equipped with a stirrer, a thermometer and two pressure-equalizing addition funnels fitted with drying tubes. The solution is cooled to -60° C. and then treated dropwise with a solution of 1.875 g (24 mmol) of dimethyl sulfoxide (distilled from calcium hydride) in 5 ml of methylene chloride over a five minute period. The reaction mixture is then stirred at -60° C. for an additional 10 minutes. A solution of 2.82 g (10 mmol) of 2-[2-(4,4-dimethylchroman-6-yl)ethynyl]-5-hydromethylpyridine in 10 ml of methylene chloride is then added to the reaction mixture over a period of 5 minutes. The mixture is stirred for a further 15 minutes and is then treated with 5.06 g (50 mmol) of triethylamine. The cooling bath is then removed and the mixture is allowed to warm to room temperature. Thirty ml of water is then added to the mixture and stirring is continued for a further 10 minutes. The organic layer is then separated and the aqueous layer is extracted with 20 ml of methylene chloride. The organic layers are then combined and washed successively with dilute HCl, water and dilute Na<sub>2</sub>CO<sub>3</sub> solution and then dried (MgSO<sub>4</sub>). The solution is then filtered and concentrated in vacuo and the residue is purified by chromatography followed by recrystallization to give the title compound.

Primary alcohols of this invention may be oxidized to their corresponding aldehyde by this method.

## EXAMPLE 31

### 2-(2-(4,4-Dimethylchroman-6-yl)ethynyl)-5-(1-hydroxypropyl)pyridine

Four ml of a 3M (12 mmol) solution of ethylmagnesium bromide in ether is placed in a 3-necked flask fitted with a mechanical stirrer, a reflux condenser protected by a drying tube and a pressure-equalizing dropping funnel protected by a drying tube. The flask is cooled in an ice bath and a solution of 2.8 g (10 mmol) of 2-(2-(4,4-Dimethylchroman-6-yl)ethynyl)pyridine-5-carboxaldehyde in 10 ml of dry ether is added slowly with vigorous stirring. The cooling bath is then removed and the mixture heated at reflux for 3 hours. The mixture is then cooled in an ice-salt bath and 5 ml of saturated ammonium chloride solution added. The mixture is stirred for a further 1 hour and then filtered and the residue washed with two 10 ml portions of ether. The ether solution is then separated, dried (MgSO<sub>4</sub>) and the ether removed in vacuo. The residue is then purified by chromatography followed by recrystallization to give the title compound.

Using the same procedure any of the other aldehydes of this invention can be converted to a secondary alcohol.

Such secondary alcohols may be converted to their corresponding ketone using the procedure recited in Example 15.

# ATTACHMENT B (cont'd)

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### EXAMPLE 32

**2-(2-(4,4-Dimethylchroman-6-yl)ethynyl)-5-dimethoxymethylpyridine**

A round-bottomed flask is fitted with a Dean-Stark apparatus under a reflux condenser protected by a drying tube. A mixture of 3.35 g (12 mmol) of 2-(4,4-dimethylchroman-6-yl)ethynyl-pyridine-5-carboxaldehyde, 4.80 mg (15 mmol) of anhydrous methanol, 2 mg of P-toluenesulfonic acid monohydrate and 10 ml of anhydrous benzene is placed in the flask and the mixture heated at reflux under nitrogen until close to the theoretical amount of water is collected in the Dean-Stark trap. The reaction mixture is cooled to room temperature and extracted successively with 5 ml of 10% sodium hydroxide solution and two 5 ml portions of water and then dried ( $MgSO_4$ ). The solution is then filtered and the solvent removed in vacuo. The residue is purified by chromatography and then recrystallization to give the title compound.

In a similar manner, any aldehyde or ketone of this invention may be converted to an acetal or a ketal.

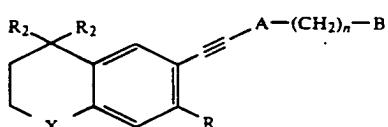
### EXAMPLE 33

Preferably, these compounds may be administered 25 topically using various formulations. Such formulation may be as follows:

Ingredient	Weight/Percent
Solution	
Retinoid	0.1
BHT 0.1	
Alcohol USP	58.0
Polyethylene Glycol 400 NF	41.8
Gel	
Retinoid	0.1
BHT 0.1	
Alcohol USP	97.8
Hydroxypropyl Cellulose	2.0

What is claimed is:

1. A compound of the formula



where *X* is S or O; *R* is hydrogen or lower alkyl; *R*<sub>2</sub> is methyl; *A* is pyridyl; *n* is 0-2; and *B* is H, -COOH or a pharmaceutically acceptable salt thereof, or an ester thereof with a saturated aliphatic alcohol of ten or fewer carbon atoms, or with a cyclic or saturated aliphatic cyclic alcohol of 5 to 10 carbon atoms, or with phenol or with a lower alkylphenol, or an amide or a mono or disubstituted amide thereof, the substituents on the amide being selected from a group consisting of saturated aliphatic radicals of ten or fewer carbon atoms, cyclic or saturated aliphatic cyclic radicals of 5 to 10 carbon atoms, and phenyl or lower alkylphenyl radicals, or *B* is CH<sub>2</sub>OH or an ester derivative thereof derived from a saturated aliphatic acid of ten or fewer carbon atoms, or from a cyclic or saturated aliphatic cyclic acid of 5 to 10 carbon atoms, or from benzoic acid, or an ether derivative thereof derived from a saturated aliphatic radical of ten or fewer carbon atoms, or from a cyclic or saturated aliphatic cyclic radical of 5 to 10 carbon atoms, or from phenyl or lower alkylphenyl radical, or *B* is -CHO or a lower alkyl acetal deriva-

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10 carbon atoms, or from phenyl or lower alkylphenyl radical, or *B* is -CHO or a lower alkyl acetal derivative thereof, or an acetal derivative thereof formed with a lower alkyl diol, or *B* is -COR<sub>1</sub> or a lower alkyl ketal derivative thereof, or a ketal derivative thereof formed with a lower alkyl diol, where R<sub>1</sub> is -(CH<sub>2</sub>)<sub>*m*</sub>CH<sub>3</sub> where *m* is 0-4, or a pharmaceutically acceptable salt of the compound defined in said formula.

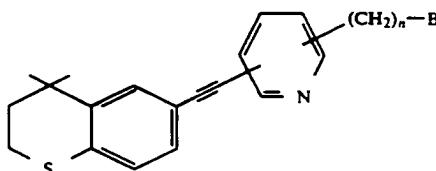
5 2. A compound of claim 1 where *X* is S, *R* is hydrogen, and *n* is 0 or 1.

10 3. A compound of claim 2 where *B* is -COOH or a pharmaceutically acceptable salt, lower alkyl ester or mono- or di-lower alkyl amide thereof.

15 4. Ethyl 6-(2-(4,4-dimethylthiochroman-6-yl)ethynyl)nicotinate.

5 5. 6-(2-(4,4-dimethylthiochroman-6-yl)ethynyl)nicotinic acid or a pharmaceutically acceptable salt thereof.

20 6. A compound of the formula



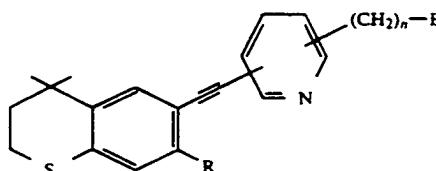
30 where *n* is 0 or 1 and where *B* is -CH<sub>2</sub>OH or a lower alkyl ether or lower alkyl acid ester thereof.

7. A compound of claim 6 which is 6-(2-(4,4-dimethylthiochroman-6-yl)-ethynyl)-3-pyridylmethanol.

8. A compound of claim 2 where *B* is -CHO or an acetal derivative thereof.

35 9. A compound of claim 8 which is 2-(2-(4,4-dimethylthiochroman-6-yl)-ethynyl)-5-pyridinecarboxaldehyde.

10. A compound of the formula



40 where *R* is lower alkyl, *n* is 0 or 1, and *B* is H, -COOH or a pharmaceutically acceptable salt thereof, or an ester thereof with a saturated aliphatic alcohol of ten or fewer carbon atoms, or with a cyclic or saturated aliphatic cyclic alcohol of 5 to 10 carbon atoms, or with phenol or with a lower alkylphenol, or an amide or a mono or di-substituted amide thereof, the substituents on the amide being selected from a group consisting of saturated aliphatic radicals of ten or fewer carbon atoms, cyclic or saturated aliphatic cyclic radicals of 5 to 10 carbon atoms, and phenyl or lower alkylphenyl radicals, or *B* is CH<sub>2</sub>OH or an ester derivative thereof derived from a saturated aliphatic acid of ten or fewer carbon atoms, or from a cyclic or saturated aliphatic cyclic acid of 5 to 10 carbon atoms, or from benzoic acid, or an ether derivative thereof derived from a saturated aliphatic radical of ten or fewer carbon atoms, or from a cyclic or saturated aliphatic cyclic radical of 5 to 10 carbon atoms, or from phenyl or lower alkylphenyl radical, or *B* is -CHO or a lower alkyl acetal deriva-

# ATTACHMENT B (cont'd)

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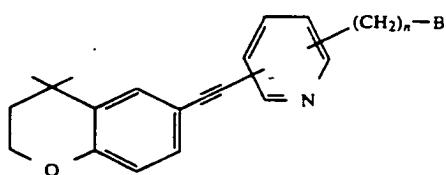
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tive thereof, or an acetal derivative thereof formed with a lower alkyl diol, or B is  $-\text{COR}_1$  or a lower alkyl ketal derivative thereof, or a ketal derivative thereof formed with a lower alkyl diol, where  $R_1$  is  $-(\text{CH}_2)_m\text{CH}_3$  where m is 0-4, or a pharmaceutically acceptable salt of the compound defined in said formula.

11. A compound of claim 10 which is 6-(2-(4,4,7-trimethylthiochroman-6-yl)ethynyl)nicotinic acid or a pharmaceutically acceptable salt thereof.

12. A compound of the formula



where n is 0 or 1, and B is H,  $-\text{COOH}$  or a pharmaceutically acceptable salt thereof, or an ester thereof with a saturated aliphatic alcohol of ten or fewer carbon atoms, or with a cyclic or saturated aliphatic cyclic alcohol of 5 to 10 carbon atoms, or with phenol or with a lower alkylphenol, or an amide or a mono or di-substituted amide thereof, the substituents on the amide being selected from a group consisting of saturated aliphatic radicals of ten or fewer carbon atoms, cyclic or saturated aliphatic cyclic radicals of 5 to 10 carbon atoms, and phenyl or lower alkylphenyl radicals, or B is  $\text{CH}_2\text{OH}$  or an ester derivative thereof derived from a saturated aliphatic acid of ten or fewer carbon atoms, or from a cyclic or saturated aliphatic cyclic acid of 5 to 10 carbon atoms, or from benzoic acid, or an ether derivative thereof derived from a saturated aliphatic radical of ten or fewer carbon atoms, or from a cyclic or saturated aliphatic cyclic radical of 5 to 10 carbon atoms, or from benzoic acid, or an ether derivative thereof derived from a saturated aliphatic radical of ten or fewer carbon atoms, or from a cyclic or saturated aliphatic cyclic radical of 5 to 10 carbon atoms, or from phenyl or lower alkylphenyl radical, or B is  $-\text{CHO}$  or a lower alkyl acetal derivative thereof, or an acetal derivative thereof formed with a lower alkyl diol, or B is  $-\text{COR}_1$  or a lower alkyl ketal derivative thereof, or a ketal derivative thereof formed with a lower alkyl diol, where  $R_1$  is  $-(\text{CH}_2)_m\text{CH}_3$  where m is 0-4, or a pharmaceutically acceptable salt of the compound defined in said formula.

13. A compound of claim 12 where B is  $-\text{COOH}$  or a pharmaceutically acceptable salt, lower alkyl ester or mono- or di-lower alkyl amide thereof.

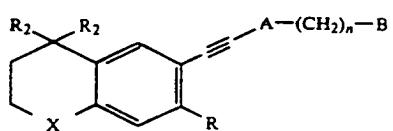
14. 6-(2-(4,4-dimethylchroman-6-yl)ethynyl)nicotinic acid or a pharmaceutically acceptable salt thereof.

15. Ethyl 6-(2-(4,4-dimethylchroman-6-yl)ethynyl)-nicotinate.

16. A compound of claim 12 where B is  $-\text{CH}_2\text{OH}$  or a lower alkyl ether or lower alkyl acid ester thereof.

17. A compound of claim 12 where B is  $-\text{CHO}$  or an acetal derivative thereof.

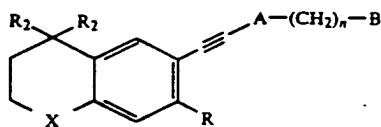
18. A pharmaceutical composition comprising a pharmaceutically acceptable excipient and a compound of the formula



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where X is S or O; R is hydrogen or lower alkyl;  $R_2$  is methyl; A is pyridyl; n is 0-2; and B is H,  $-\text{COOH}$  or a pharmaceutically acceptable salt thereof, or an ester thereof with a saturated aliphatic alcohol of ten or fewer carbon atoms, or with a cyclic or saturated aliphatic cyclic alcohol of 5 to 10 carbon atoms, or with phenol or with a lower alkylphenol, or an amide or a mono or di-substituted amide thereof, the substituents on the amide being selected from a group consisting of saturated aliphatic radicals of ten or fewer carbon atoms, cyclic or saturated aliphatic cyclic radicals of 5 to 10 carbon atoms, and phenyl or lower alkylphenyl radicals, or B is  $\text{CH}_2\text{OH}$  or an ester derivative thereof derived from a saturated aliphatic acid of ten or fewer carbon atoms, or from a cyclic or saturated aliphatic cyclic acid of 5 to 10 carbon atoms, or from benzoic acid, or an ether derivative thereof derived from a saturated aliphatic radical of ten or fewer carbon atoms, or from a cyclic or saturated aliphatic cyclic radical of 5 to 10 carbon atoms, or from phenyl or lower alkylphenyl radical, or B is  $-\text{CHO}$  or a lower alkyl acetal derivative thereof, or an acetal derivative thereof formed with a lower alkyl diol, or B is  $-\text{COR}_1$  or a lower alkyl ketal derivative thereof, or a ketal derivative thereof formed with a lower alkyl diol, where  $R_1$  is  $-(\text{CH}_2)_m\text{CH}_3$  where m is 0-4, or a pharmaceutically acceptable salt of the compound defined in said formula.

19. A method of treating psoriasis in a mammal which method comprises administering alone or in conjunction with a pharmaceutically acceptable excipient, a therapeutically effective amount of a compound of the formula



where X is S or O; R is hydrogen or lower alkyl;  $R_2$  is methyl; A is pyridyl; n is 0-2; and B is H,  $-\text{COOH}$  or a pharmaceutically acceptable salt thereof, or an ester thereof with a saturated aliphatic alcohol of ten or fewer carbon atoms, or with a cyclic or saturated aliphatic cyclic alcohol of 5 to 10 carbon atoms, or with phenol or with a lower alkylphenol, or an amide or a mono or di-substituted amide thereof, the substituents on the amide being selected from a group consisting of saturated aliphatic radicals of ten or fewer carbon atoms, cyclic or saturated aliphatic cyclic radicals of 5 to 10 carbon atoms, and phenyl or lower alkylphenyl radicals, or B is  $\text{CH}_2\text{OH}$  or an ester derivative thereof derived from a saturated aliphatic acid of ten or fewer carbon atoms, or from a cyclic or saturated aliphatic cyclic acid of 5 to 10 carbon atoms, or from benzoic acid, or an ether derivative thereof derived from a saturated aliphatic radical of ten or fewer carbon atoms, or from a cyclic or saturated aliphatic cyclic radical of 5 to 10 carbon atoms, or from phenyl or lower alkylphenyl radical, or B is  $-\text{CHO}$  or a lower alkyl acetal derivative thereof, or an acetal derivative thereof formed with a lower alkyl diol, or B is  $-\text{COR}_1$  or a lower alkyl ketal derivative thereof, or a ketal derivative thereof formed with a lower alkyl diol, where  $R_1$  is  $-(\text{CH}_2)_m\text{CH}_3$  where m is 0-4, or a pharmaceutically acceptable salt of the compound defined in said formula.

\* \* \* \*

# ATTACHMENT C

Page 32  
CLIENT'S COPY

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Only!

PRINTER'S TRIM LINE

## UNITED STATES PATENT AND TRADEMARK OFFICE CERTIFICATE OF CORRECTION

PATENT NO. : 5,089,509

Page 1 of 1

DATED : February 18, 1992

INVENTOR(S) : Roshantha A.S. Chandraratna

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Column 17, line 64, "mgSO<sub>4</sub>" should be --MgSO<sub>4</sub>--;

Column 19, line 45, "5)5" should be --5(5--;

Column 26, line 30, "hopurs" should be --hours--.

MAILING ADDRESS OF SENDER: 400-26-CIP  
Law Offices

KLEIN & SIEKERES  
4199 Campus Drive  
Suite 700  
Irvine, CA 92715

FORM PTO 1050 (REV. 3-82)

PATENT NO. 5,089,509

No. of add'l. copies  
@ 30¢ per page



# ATTACHMENT D

Page 33



UNITED STATES DEPARTMENT OF COMMERCE  
Patent and Trademark Office  
Address: COMMISSIONER OF PATENTS AND TRADEMARKS  
Washington, D. C. 20231

PAYOR NUMBER  
000204

75M7/0824  
COMPUTER PACKAGES ANNUITY SERVICE INC.  
414 HUNTERFORD DRIVE, SUITE 300  
ROCKVILLE, MD 20850

AA 16561 USA SUB C1 AUG 95

## MAINTENANCE FEE STATEMENT

The data shown below is from the records of the Patent and Trademark Office. If the maintenance fees and any necessary surcharges have been timely paid for the patents listed below, the notation "PAID" will appear in column 10, "status" below.

If a maintenance fee payment is defective, the reason is indicated by code in column 10, "status" below. An explanation of the codes appears on the reverse of the Maintenance Fee Statement. TIMELY CORRECTION IS REQUIRED IN ORDER TO AVOID EXPIRATION OF THE PATENT. NOTE 37 CFR 1.377. THE PAYMENT(S) WILL BE ENTERED UPON RECEIPT OF ACCEPTABLE CORRECTION. IF PAYMENT OR CORRECTION IS SUBMITTED DURING THE GRACE PERIOD, A SURCHARGE IS ALSO REQUIRED. NOTE 37 CFR 1.20(k) and (l).

If the statement of small entity status is defective the reason is indicated below in column 10 for the related patent number. THE STATEMENT OF SMALL ENTITY STATUS WILL BE ENTERED UPON RECEIPT OF ACCEPTABLE CORRECTION.

ITEM NBR	PATENT NUMBER	FEE CDE AMOUNT	FEE AMOUNT	SUR CHARGE	SERIAL NUMBER	PATENT DATE	FILE DATE	PAY SML YR ENT STAT
1	5,089,509	183	960	----	07/326,191	02/18/92	03/20/89	04 NO PAID

If the "status" column for a patent number listed above does not indicate "PAID" a code or an asterisk (\*) will appear in the "status" column. Where an asterisk (\*) appears, the codes are set out below by the related item number. An explanation of the codes indicated in the "status" column and as set out below by the related item number appears on the reverse of the maintenance fee statement.

ITM NR	ATY DKT NUMBER
-----------	-------------------

-----1----- 16561CIP

DIRECT THE RESPONSE TOGETHER WITH ANY QUESTIONS ABOUT THIS NOTICE TO:

# **ATTACHMENT E**

Page 34

## STATEMENT IN ACCORDANCE WITH 37 CFR § 1.740(a)(10)

(a) U.S. Patent No. 5,089,509 issued on February 18, 1992.

(b) Application for investigation New Drug Exemption (IND) for Tazarotene (Tazorac®) gel was effective on February 16, 1990 IND. No. 34-212.

(c) New Drug Application (NDA) for Tazarotene (Tazorac®) was initially submitted on June 19, 1995 as NDA 20-600.

(d) NDA 20-600 for Tazarotene (Tazorac®) was approved on June 13, 1997.

## **ATTACHMENT F**

Brief Description, in accordance with 37 CFR 1.740(11), of significant activities undertaken by marketing applicant during regulatory review period with respect to TAZORAC®.

On January 16, 1990, IND 34-212 was filed with the Food and Drug Administration in accordance with the applicable laws and regulations to enable Allergan to test its proprietary retinoid compound, Tazarotene, for treating acne and psoriasis in human patients. In accordance with the FDA regulations, this IND became active on February 16, 1990. (The FDA requested a correction of the cover sheet of such IND which was submitted on January 12, 1990.)

Subsequently, the FDA requested additional information regarding the formulations which were to be tested under such IND and also pointed out there were certain pages missing from a submitted Pharmacokinetic Study. Allergan responded by filing Amendments on March 13, 1990, and May 18, 1990, respectively, to correct these omissions. A further Amendment was submitted to the FDA on July 26, 1990, to provide an additional Pharmacokinetic Study, a Toxicology Study and a Summary of Human Study Results, including an Updated Investigators Brochure and New Investigator Data. On August 31, 1990, Allergan filed a Phase I Clinical Information Amendment which included a final report for a Human Clinical Study that had been completed. Subsequently, on October 4, 1990, another report of a completed Human Clinical Study was filed. On February 22, 1991, Allergan filed a Human Pharmacokinetic Clinical Protocol Submission. The Annual Report, which is due 60 days from the anniversary of the effective date of the IND, was filed in a timely fashion on February 28, 1991.

A new Protocol, directed to the treatment of human patients suffering from acne and/or psoriasis, as opposed to healthy volunteers, and a Protocol for an In-vitro assay of blood plasma for presence of the active ingredient of TAZORAC®, i.e., Tazarotene, was filed on August 2, 1991. On September 27, 1991, a final report of another Human Clinical Study was filed. This Study was labeled "R168-110-8225." On October 29, 1991, Allergan filed an Amendment presenting monkey pharmacokinetic data as a final report. December 20, 1991, a Clinical Protocol was submitted for human clinical pharmacokinetic data. In response to a request from the FDA, Allergan filed on January 29, 1992, an in-progress Toxicology and Pharmacokinetic Information Statement and proposed Amendments to determine the status of Allergan's clinical studies on TAZORAC®. Allergan requested a meeting with the FDA on its non-clinical development plan on March 12, 1992. On March 20, 1992, Allergan withdrew the Toxicology and Pharmacokinetic Information Statement that was filed on January 29, 1992 due to Allergan's desire to reschedule the meeting to include Allergan personnel not available on March 12, 1992. Because of the workload resulting from the clinical development of another Allergan dermatological product, Allergan notified the FDA on April 16, 1992 that there would be a delay in filing the Annual Progress Report. On May 12, 1992, Allergan filed an Amendment to the IND and a corrected FDA 1571 Form. The IND Annual Progress Report was ultimately filed on June 10, 1992.

Allergan met with the FDA on June 4, 1992, to discuss its pre-clinical development plans. The minutes from this meeting were sent to the FDA on June 24, 1992. (Since it had not been submitted earlier, on November 17, 1992, Allergan faxed the FDA the agenda for this meeting.) On August 12, 1992, Allergan filed an Information Amendment which updated the Clinical Investigators Brochure, and provided a non-clinical pharmacokinetic final report. On August 20, 1992, Allergan requested a meeting to discuss the end-of-Phase II data. On September 23, 1992, Allergan filed a Dose Ranging Carcinogenicity Study Final Report for Rats. Allergan provided information to the FDA for the requested end of Phase II meeting, by separate

communications dated November 18 and December 8, 1992. This meeting was held on December 10, 1992 and the minutes were filed on February 10, 1993. On June 16, 1993, Allergan mailed the minutes and summary of the above meeting with the FDA on December 10, 1992. The IND Annual Report was again delayed, due to the workload of Allergan personnel, therefore FDA was notified on April 7, 1993 of such late filing as permitted by FDA Regulations. On May 5, 1993, Allergan filed a Protocol Amendment and a New Protocol for a Pivotal Study, designated as R168-120-8606. On June 15, 1993, it was necessary to file an IND Safety Report as a result of a heart-attack death of a patient in a clinical trial with TAZORAC<sup>®</sup>; however, the use of TAZORAC<sup>®</sup> was not implicated in this incident. On July 13, 1993, Allergan filed the Annual Progress Report and Amendments. This included Final Reports on Clinical Trials R168-150-7997, and R168-120-8225 entitled Percutaneous absorption and mass balance of <sup>14</sup>C-AGN 190168 0.1% gel following topical administration to healthy subjects and Safety and efficacy of once-daily AGN 190168 in the treatment of acne vulgaris: AGN 190168 0.05% and 0.1% gels versus vehicle gel, respectively. (Note AGN 190168 is Allergan's in-house designation for Tazarotene.) The following pre-clinical reports were also filed at this time:

- Final Report:** 1643B 2667.17: Acute, single dose topical skin toxicity study in male and female rats with various concentrations of AGN 190168 gels followed by fourteen days of observations.
- Final Report:** 1643B-1667-15: Acute, single dose toxicity study (intact-occluded) in the male and female rabbits and various concentrations of AGN 190168 gels followed by 14 days of observations.
- Final Report:** 440A-601-234-91; A three month dermal toxicity study of AGN 190168 in Hanford miniswine.
- Final Report:** HWA 985 120: A six month oral toxicity study of AGN 190168 in monkeys with a recovery period.
- Final Report:** ALG 18/920710: AGN 190168--Preliminary toxicity study in rats by repeated dietary administration for 13 weeks.

**Final Report:** 1643B-2667-16: Acute single dose toxicity study (abrade-occluded) in male and female rabbits with various concentrations of AGN 190168 gels followed by 14 days of observations.

**Final Report:** SLS 3202.7: A dermal fertility and general reproduction study in rats with AGN 190168 (segment I).

**Final Report:** 1643-1725-2: Six month skin toxicity study of multiple topical applications with preparations of AGN 190168 in male and female rats.

**Summary Report:** C-1801-001P: Dose selection for photocarcinogenicity study in hairless mice.

On September 23, 1993, a Toxicology Information Amendment was filed. This Amendment included the following:

**Protocol:** Dose selection for dermal carcinogenicity study in mice.

**Final Report:** Range finding Tolerance Study of AGN 190168 (topical) in albino hairless mice (for photocarcinogenicity study).

**Final Report:** A dermal prenatal and postnatal study in rats with AGN 190168 (segment III).

On October 21, 1993, a Clinical Information Amendment was filed. This Amendment included the following studies:

1. R168-121-8606: Safety and efficacy of once-daily AGN 190168 0.1% Gel or 0.05% Gel versus vehicle gel in stable plaque psoriasis.
2. R168-125-8606: Safety, efficacy and duration of therapeutic effect of AGN 190158 0.1% or 0.05% Gel applied once-daily versus Lidex<sup>®</sup> (fluocinonide) 0.05% Cream applied twice-daily in stable plaque psoriasis.
3. R179-126-8606: Safety, efficacy and duration of therapeutic effect of AGN 190158 0.1% or 0.05% Gel applied once-daily versus Lidex<sup>®</sup> (fluocinonide) 0.05% Cream applied twice-daily in stable plaque psoriasis.

4. R168-221-8606: Safety and efficacy of AGN 190168 in the treatment of acne vulgaris: AGN 190168 0.1% and 0.05% Gels versus vehicle gel.

On March 29, 1994, Allergan filed the IND Safety Report and, on April 1, 1994, a Notice that the IND Annual Report would be delayed was submitted to the FDA. The IND Annual Report along with the Toxicology Information Amendment was ultimately filed on June 17, 1994. This report included a clinical update on studies R120, 121, 125, 126 and 128. The following final reports were also submitted:

**Clinical Update:** R168-120, 121, 125, 126, 128

**Final Reports:**

**Study #1643B-2970-3:** AGN 190168, Single dose ocular safety study in albino rabbits

**Study #1643B-2970-5:** AGN 190168, Single dose infusion study in albino rabbits

**Study #440B-602-244-91:** 12 Month dermal toxicity study of AGN 190168 in Handford miniswine

**Study #PK-94-031:** Tissue distribution of radioactivity following a single interavenous dose

**Study #PK-94-040:** Skin distribution of <sup>14</sup>C-AGN 190168 following single and multiple topical administration of a 0.1% gel to the skin of male mini pigs

Also, on June 17, 1994, a Toxicology Information Amendment was submitted to the FDA, which informed the FDA of changes to the Protocol for the 18-Month Dermal Carcinogenicity Study In Mice. On July 19, 1994, Allergan requested a pre-NDA meeting, and provided background data for that meeting on September 1, 1994. This meeting was held on October 24, 1994, and the minutes were submitted to the FDA on November 3, 1994.

On November 22, 1994, Allergan filed an Amendment to the Chemical Manufacturing Control regarding validation of the bulk drug substance. On December 8, 1994,

Allergan filed a Clinical Information Amendment for a new route of administration of Tazarotene, that is I.V. Dosing. The Annual Progress Report was filed timely on March 13, 1995. A Toxicology Information Amendment was filed on April 10, 1995, which reported the end of the Mouse Carcinogenicity Study at 21 months.

On June 16, 1995, a New Drug Application, NDA 20-600, was filed and accepted three days later, on June 19, 1995.

Allergan received a Not Approvable Letter of its NDA on June 6, 1996 (a copy of which is attached hereto), which raised Chemical, Manufacturing and Control (CMC), Bio Pharmaceutics, Microbiology, Clinical and Pharmacology issues. Allergan responded to this Not Approvable Letter on June 27, 1996, and subsequently received an Approvable Letter on December 30, 1996 (a copy of which is attached hereto). The only issues remaining were labeling, pregnancy issues, and issues concerning the pharmacokinetic profile. Allergan responded to this Approvable Letter on January 17, 1997, and submitted a new Pharmacokinetic Study which overcame certain of the labeling issues and resulted in a more accurate pharmacokinetic profile for TAZORAC<sup>®</sup>.

Allergan received its Approval Letter on June 13, 1997 timely (a copy of which is attached hereto).

The above incidents and dates are set forth in Exhibit A, which is attached to and made a part of this Attachment F

**EXHIBIT**

A

TAZORAC®

IND 34,212

<u>SUBJECT/CONTENT</u>	<u>DATE SUBMITTED</u>	<u>SERIAL NUMBER</u>
The Investigational New Drug Application (IND) was filed	01/16/90	000
Replacement Cover Sheet for IND	01/12/90	001
Amendment	03/13/90	002
Amendment	05/18/90	003
Amendment	07/26/90	004
Phase I Clinical Information Amendment	08/31/90	005
Phase I Clinical Information Amendment	10/94/90	006
Clinical Protocol Submission	02/22/91	007
Annual Report	02/28/91	008
Clinical & Pharmacokinetics Amendments	08/02/91	009
Final Report of Study R168-110-8225	09/27/91	010
Pharmacokinetic Amendment	10/29/91	011
Clinical Protocol Submission	12/20/91	012
Toxicology and Pharmacokinetics Amendment	01/29/92	013
Request for FDA Meeting	03/12/92	013B
Toxicology and withdrawal of Document Serial No. 013	03/20/92	014
Notice of Delay in the Annual Filing Report	04/16/92	015
Amendment to IND (Corrected FDA 1571)	05/12/92	017
IND Annual Progress Report	06/10/92	018
Meeting minutes from 6/4/92 FDA meeting	06/24/92	019
Pharmacokinetic and Clinical Amendments	08/12/92	020
Request for End of Phase II Meeting	08/20/92	021
Dose Ranging Carcinogenicity Study (Rats)	09/23/92	022
Agenda for End of Phase II Meeting	11/17/92	
Information for End of Phase II Meeting	11/18/92	023
Information for End of Phase II Meeting	12/08/92	024
Minutes of End of Phase II Meeting	02/10/93	025
Delay in Filing Annual Report	04/07/93	026

**EXHIBIT**

A

TAZORAC®

IND 34,212

Page -2-

<u>SUBJECT/CONTENT</u>	<u>DATE SUBMITTED</u>	<u>SERIAL NUMBER</u>
Protocol Amendment/New Protocol	05/05/93	027
IND Safety Report	06/15/93	028
Minutes/Summary of End of Phase II Meeting	06/16/93	029
Annual Report & Amendments	07/13/93	030
Toxicology Amendment	09/23/93	031
Clinical Amendments	10/21/93	032
IND Safety Report	03/29/94	033
Delay in Filing Annual Report	04/01/94	034
IND Annual Report & Toxicology Amendments	06/17/94	035
Toxicology Amendment	06/17/94	036
Request for Pre-NDA Meeting	07/19/94	037
Background data for Pre-NDA Meeting	09/01/94	038
Reschedule Pre-NDA Meeting	09/24/94	039
Pre-NDA Meeting Minutes	11/03/94	040
CMC Amendment	11/22/94	041
Clinical Information Amendment	12/08/94	042
Annual Report	03/13/95	043
Toxicology Amendment	04/10/95	044
NDA was Accepted for Filing	06/19/95	
Not Approvable Letter Received	06/06/96	
Response to Not Approvable Letter	06/27/96	
Approvable Letter Received	12/30/96	
Response to Approvable Letter	01/17/97	
Approval Letter Received	06/13/97	



## DEPARTMENT OF HEALTH &amp; HUMAN SERVICES

Public Health Service

NDA 20-600

Food and Drug Administration  
Rockville MD 20857

Allergan, Inc.

Attention: Trudy A. Rumbaugh, M.D.  
 Director, Global Regulatory Affairs, Retinoids  
 2525 Dupont Drive  
 P.O. Box 19534  
 Irvine, CA 92713-9534

RECEIVED

DEC 30 1996

DEC 31 1996

ALLEGAN PHARMACEUTICALS  
REGULATORY AFFAIRS

Dear Dr. Rumbaugh:

Please refer to your June 16, 1995, New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Tazorac (tazarotene gel) Topical Gel, 0.05% and 0.1%.

Please refer to your Not Approvable letter dated June 6, 1996.

We acknowledge receipt of your amendments and correspondence dated June 27, and 28, July 11, 22, and 30, September 4, and 18, October 18, and 29, November 14, 18, and 26, December 2, 4, 5, and 11, 1996.

This new drug application provides for the treatment of acne vulgaris and plaque psoriasis.

We have completed the review of this application as submitted with the draft labeling of June 22, 1995. Tazarotene gel, 0.05%, is approvable for the daily topical treatment of stable plaque psoriasis covering not more than 20% of body surface area. Tazarotene gel, 0.1%, is approvable for the daily topical treatment of stable plaque psoriasis covering not more than 20% of body surface area and in the treatment of mild to moderate facial acne vulgaris. Before this application may be approved, however, it will be necessary for you to submit the following information:

1. Revised draft labeling identical in content to the enclosed draft labeling. The proposed Tradename, Tazorac, for this drug product, was found acceptable.
2. Although study R168-146-8606, a phase 3 trial being conducted in the U.K., has not been unblinded, available safety data is needed. 110/91
3. The Study Report for R168-722-8606 has been submitted previously. The only additional information in this submission was a Table of ALL adverse events shown in the Safety Update (Safety Update Table 2c from 6/27/96 submission, p. 1-050). The data from the table does not agree with that in the study report (Table 8 of study report, p. 4-069 of 6/27/96 submission). The differences should be explained.

NDA 20-600

Page 2

4. In R168-128-8606, documentation of an allergic component was not presented. You subsequently argued that the reactions represent local irritation produced by tazarotene gel. However, this is still classified as an allergic contact dermatitis in the data analysis. A correction of this is needed.
5. An analysis is needed of the age subsets within those patients less than 45 years of age in acne studies.
6. Information on follow-up of the three babies born of mothers who became pregnant while being treated with tazarotene in the clinical trials is needed. In addition, plasma drug levels from subject C14 in Study R168-221-8606 taken when pregnancy was discovered should be presented.
7. Please submit a commitment to conduct the following Phase 4 Study within 6 months of an Approval Letter:

A pharmacokinetic study clarifying the systemic exposure to and distribution of AGN 190299, the active metabolite of tazarotene, following long term use in psoriatic patients.

Protocols, data, and final reports should be submitted to your IND for this product and a copy of the submission also submitted to the NDA.

Should an IND not be required to meet your Phase 4 commitment, please submit protocol, data, and final reports to this NDA as correspondences. For administrative purposes, all submissions, including labeling supplements, relating to Phase 4 commitments must be clearly designated "Phase 4 Commitments."

8. Please submit a commitment to provide the following:
  - a. A follow-up on the incidence of photosensitivity associated with long-term use of tazarotene.
  - b. Establishment of a registry for women who become pregnant while being treated with tazarotene and submit reports on follow-up of these women and the babies subsequently born.
  - c. A description of the scale-up procedures for the bulk drug substance at the Torcan and Cambridge manufacturing facilities.

NDA 20-600

Page 3

- d. The results of a gender analysis on PK study 190168-004 should be submitted when the study is completed.

Under 21 CFR 314.50(d)(5)(vi)(b), we request that you update your NDA by submitting all safety information you now have regarding your new drug. Please provide updated information as listed below:

1. Retabulate all safety data including results of trials that were still ongoing at the time of NDA submission. The tabulation can take the same form as in your initial submission. Tables comparing adverse reactions at the time the NDA was submitted vs now will certainly facilitate review.
2. Retabulate drop-outs with new drop-outs identified. Discuss, if appropriate.
3. Provide details of significant changes or findings, if any.
4. Summarize worldwide experience on the safety of this drug.
5. Submit case report forms for each patient who died during a clinical study or who did not complete a study because of an adverse event.

Please also update the new drug application with respect to reports of relevant safety information, including all deaths and any adverse events that led to discontinuation of the drug and any information suggesting a substantial difference in the rate of occurrence of common but less serious adverse events. The update should cover all studies and uses of the drug including: (1) those involving indications not being sought in the present submission, (2) other dosage forms, and (3) other dose levels, etc.

Validation of the regulatory methods has not been completed. At the present time, it is the policy of the Center not to withhold approval because the methods are being validated. Nevertheless, we expect your continued cooperation to resolve any problems that may be identified.

In addition, please submit three copies of the introductory promotional material that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print. Please submit one copy to this Division and two copies of both the promotional material and the package insert directly to:

NDA 20-600

Page 4

Food and Drug Administration  
Division of Drug Marketing, Advertising and Communications,  
HFD-40  
5600 Fishers Lane  
Rockville, Maryland 20857

Within 10 days after the date of this letter, you are required to amend the application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. In the absence of such action FDA may take action to withdraw the application.

The drug may not be legally marketed until you have been notified in writing that the application is approved.

Should you have any questions, please contact:

Frank H. Cross, Jr., M.A., LCDR  
Project Manager  
Telephone: (301) 827-2020

Sincerely yours,

*Michael Weintraub 11/7/976*

Michael Weintraub, M.D.  
Director  
Office of Drug Evaluation V  
Center for Drug Evaluation and Research

Enclosure

The reviewers for this application consisted of:

Jonathan K. Wilkin, M.D., Division Director, DDDDP, HFD-540  
Linda Katz, M.D., Deputy Division Director, DDDDP, HFD-540  
Hon-Sum Ko, M.D., Medical Officer, DDDDP, HFD-540  
R. Srinivasan, Ph.D., Biostatistics Team Leader, DOBIV, HFD-725  
Steve Thomson, Ph.D., Biostatistician, DOBIV, HFD-725  
Abby Jacobs, Ph.D., Pharmacology/Toxicology Team Leader, DDDDP, HFD-540  
Hilary Sheevers, Ph.D., Toxicologist, DDDDP, HFD-540  
Amy Nostrandt, D.V.M., Ph.D., Toxicologist, DDDDP, HFD-540  
Eric Sheinin, Ph.D., Director, DNDCIII, HFD-830  
Wilson DeCamp, Ph.D., Chemistry Team Leader, DNDCIII, HFD-540  
Sydney Gilman, Ph.D., Chemist, DNDCII, HFD-160  
Dennis Bashaw, Ph.D., Biopharmaceutics Team Leader, DPEIII, HFD-880  
Sue-Chih Lee, Ph.D., Biopharmaceuticist, DPEIII, HFD-880  
Peter Cooney, Ph.D., Microbiology Supervisor, ONDC, HFD-805  
Patricia Hughes, Ph.D., Microbiologist, ONDC, HFD-805  
Maria Rossana R. Cook, M.B.A., Supervisory Project Manager, DOTCDE, HFD-560  
Mary Jean Kozma-Fornaro, R.N., M.S.A., Supervisory Project Manager, DDDDP, HFD-540  
Frank Cross, Jr., M.A., LCDR, Regulatory Management Officer, DDDDP, HFD-540

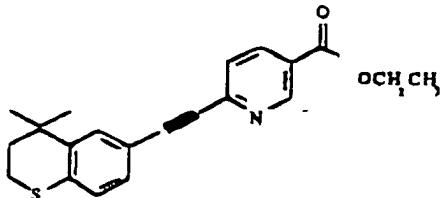
**TAZORAC™**  **ALLERGAN**  
**(tazarotene gel) Topical Gel, 0.1%**  
**(tazarotene gel) Topical Gel, 0.05%**

---

**FOR DERMATOLOGIC USE ONLY**  
**NOT FOR OPHTHALMIC USE**

**DESCRIPTION:**

TAZORAC™ is a translucent, aqueous gel and contains the compound tazarotene, a member of the acetylenic class of retinoids. It is for topical dermatologic use only. The active ingredient is represented by the following structural formula:



**TAZAROTENE**  
 $C_{21}H_{21}NO_2S$

Molecular Weight: 351.46

Chemical Name: ethyl 6-[2-(4,4-dimethylthiochroman-6-yl)-ethynyl] nicotinate

**Contains:**

**Active:** Tazarotene..... 0.1% or 0.05% (w/w)

**Preservative:** Benzyl alcohol..... 1.0% (w/w)

**Inactives:** Ascorbic acid, butylated hydroxyanisole, butylated hydroxytoluene, carbomer 934P, edetate disodium, hexylene glycol, purified water, poloxamer 407, polyethylene glycol 400, polysorbate 40, and tromethamine.

**CLINICAL PHARMACOLOGY:**

Tazarotene is a retinoid prodrug which is converted to its active form, the cognate carboxylic acid of tazarotene (AGN 190299), by rapid deesterification in most biological systems. AGN 190299 binds to all three members of the RAR family of retinoid nuclear receptors, RAR $\alpha$ , RAR $\beta$ , and RAR $\gamma$ , but shows relative selectivity for RAR $\beta$  and RAR $\gamma$  and may modify gene expression. The clinical significance of these findings is unknown.

**Psoriasis:** The mechanism of tazarotene action in psoriasis is not defined. Topical tazarotene blocks induction of mouse epidermal ornithine decarboxylase (ODC) activity, which is associated with cell proliferation and hyperplasia. In cell culture and in vitro models of skin, tazarotene suppresses expression of MRP8, a marker of inflammation present in the epidermis of psoriasis subjects at high levels. In human keratinocyte cultures, it inhibits cornified envelope formation, whose build-up is an element of the psoriatic scale. The clinical significance of these findings is unknown.

**Acne:** The mechanism of tazarotene action in acne is not defined. Tazarotene inhibited corneocyte accumulation in rhino mouse skin and cross-linked envelope formation in cultured human keratinocytes. The clinical significance of these findings is unknown.

**Pharmacokinetics:**

Following topical application, tazarotene undergoes esterase hydrolysis to form its active metabolite, AGN

190289. The human *in vivo* studies described below were conducted with the 0.1% gel applied topically at approximately 2 mg/cm<sup>2</sup> and left on the skin for 10 to 12 hours. Both the peak plasma concentration (C<sub>max</sub>) and area under the plasma concentration-time curve (AUC) refer to the active metabolite only. Very little parent compound could be detected in the plasma.

Two single, topical dose studies were conducted using <sup>14</sup>C-tazarotene gel. Systemic absorption as determined from radioactivity in the excreta was less than 1% of the applied dose in psoriatic patients without occlusion (n=6), and approximately 5% of the applied dose in healthy subjects under occlusion (n=6).

After 7 days of topical dosing on 20% of total body surface in healthy subjects without occlusion (n=24), the mean C<sub>max</sub> was 0.72±0.58 ng/mL occurring 9 hours after dose application, and the mean AUC<sub>0-24 hr</sub> was 10.1±7.2 ng·hr/mL. Systemic absorption was estimated to be up to 4% of the applied dose.

Upon repeated topical applications to lesional skin in psoriatic patients (n=5), systemic absorption was substantially greater. After 14 days of topical dosing without occlusion on involved skin (8 to 18% of total body surface area; mean: 13±5%), the mean C<sub>max</sub> was 12.0±7.6 ng/mL occurring 6 hours after topical application and the mean AUC<sub>0-24 hr</sub> was 105±55 ng·hr/mL. Extrapolation of these results to represent dosing on 20% of total body surface yielded a mean C<sub>max</sub> of 18.9±10.6 ng/mL and mean AUC<sub>0-24 hr</sub> of 172±88 ng·hr/mL. As much as 25% of the applied dose could be absorbed in some patients.

The active metabolite, AGN 190299, is highly bound to plasma proteins (>99%) and has an apparent plasma half-life of approximately 18 hours. Oxidative metabolism of tazarotene and the active metabolite forms sulfoxides, sulfones and other polar metabolites. Both urinary and fecal pathways were found to be equally important for the excretion of tazarotene and metabolites.

In vitro percutaneous absorption studies, using radiolabeled drug and freshly excised human skin or human cadaver skin, indicated that approximately 4 to 5% of the applied dose was in the stratum corneum (tazarotene: AGN 190299=5:1) and 2 to 4% was in the viable epidermis-dermis layer (tazarotene: AGN 190299=2:1) 24 hours after topical application of the gel.

#### CLINICAL STUDIES:

##### Psoriasis:

In two large vehicle-controlled clinical studies, tazarotene 0.1% and 0.05% gels applied once daily were significantly more effective than vehicle in reducing the severity of the clinical signs of stable plaque psoriasis covering less than 20% of body surface area. Differences from baseline (reductions) after treatment of lesions for 12 weeks in these two studies are shown in the following Table:

	TAZORAC™, 0.05% Gel (N=108; 111)				TAZORAC™, 0.1% Gel (N=108; 112)				Vehicle Gel (N=108; 113)			
	Trunk/Arm/Leg lesions		Knee/Elbow lesions		Trunk/Arm/ Leg lesions		Knee/Elbow lesions		Trunk/Arm/ Leg lesions		Knee/Elbow lesions	
Plaque elevation	-1.4	-1.3	-1.3	-1.1	-1.4	-1.4	-1.5	-1.3	-0.8	-0.7	-0.7	-0.6
Scaling	-1.1	-1.1	-1.1	-0.9	-1.3	-1.3	-1.2	-1.2	-0.7	-0.7	-0.6	-0.6
Erythema	-1.0	-0.8	-0.9	-0.8	-1.0	-1.1	-1.0	-0.8	-0.6	-0.5	-0.5	-0.5

Plaque elevation, scaling and erythema scored on a 0-3 scale with 0=none, 1=mild, 2=moderate and 3=severe.

Global improvement of 50% or more over baseline at the end of 12 weeks of treatment in these two studies is shown in the following Table:

	TAZORAC™, 0.05% Gel	TAZORAC™, 0.1% Gel	Vehicle Gel
100% improvement	2/81; 1/93	0/79; 0/69	1/84; 0/81
≥ 75% improvement	23/81; 17/93	30/79; 17/69	10/84; 9/91
≥ 50% improvement	42/81; 39/93	51/79; 36/69	28/84; 21/91
No change or worse	18/81; 22/93	10/79; 10/69	29/84; 38/91

The 0.1% gel was more effective than the 0.05% gel, but the 0.05% gel was associated with less local irritation than the 0.1% gel (see ADVERSE REACTIONS section).

#### Acne:

In two large vehicle-controlled studies, tazarotene 0.1% gel applied once daily was significantly more effective than vehicle in the treatment of facial acne vulgaris of mild to moderate severity. Percent reductions in lesion counts after treatment for 12 weeks in these two studies are shown in the following Table:

	TAZORAC™ 0.1% Gel (N=150; 149)	Vehicle Gel (N=148; 149)
Noninflammatory lesions	-55%; -43%	-35%; -27%
Inflammatory lesions	-42%; -47%	-30%; -28%
Total lesions	-52%; -45%	-33%; -27%

Global improvement of 50% or more over baseline at the end of 12 weeks of treatment in these two studies is shown in the following Table:

	TAZORAC™, 0.1% Gel	Vehicle Gel
100% improvement	1/105; 0/117	0/117; 0/110
≥ 75% improvement	40/105; 21/117	23/117; 11/110
≥ 50% improvement	71/105; 56/117	47/117; 32/110
No change or worse	11/105; 12/117	22/117; 32/110

#### INDICATIONS AND USAGE:

TAZORAC™ (tazarotene gel) Topical Gel, 0.05% and 0.1%, are indicated for the topical treatment of patients with stable plaque psoriasis of less than 20% surface area involvement.

TAZORAC™ (tazarotene gel) Topical Gel, 0.1%, is also indicated for the topical treatment of patients with facial acne vulgaris of mild to moderate severity.

The efficacy of TAZORAC™ in the treatment of acne previously treated with other retinoids or resistant to oral antibiotics has not been established. Safety has NOT been established for treatment of body surface areas greater than 20%.

#### **CONTRAINDICATIONS:**

Retinoids may cause fetal harm when administered to a pregnant woman. In rats, tazarotene 0.05%, administered topically during gestation days 6 through 17 at 0.25 mg/kg/day (1.5 mg/m<sup>2</sup>/day) resulted in reduced fetal body weights and reduced skeletal ossification. Rabbits dosed topically with 250 µg/kg/day (2.75 mg/m<sup>2</sup>/day) tazarotene during gestation days 6 through 18 were noted with single incidences of known retinoid malformations, including spina bifida, hydrocephaly, and heart anomalies. As with other retinoids, teratogenic effects and post-implantation fetal loss were seen when tazarotene was given orally to rats and rabbits at doses producing ~ 3 and ~ 15 times, respectively, the systemic exposure (AUC<sub>0-24 hr</sub>) in human psoriasis patients, when extrapolated for topical treatment of 20% of body surface area. **THUS, SYSTEMIC EXPOSURE IN TOPICALLY TREATED PSORIASIS PATIENTS (FOR USE ON UP TO 20% OF BODY SURFACE AREA) COULD BE IN THE SAME ORDER OF MAGNITUDE AS IN THESE ORALLY TREATED ANIMALS.** Systemic exposure anticipated in the treatment of facial acne may be less, due to a more limited area of application. When rats were administered 0.25 mg/kg/day (1.5 mg/m<sup>2</sup>/day) of tazarotene orally, developmental delays were noted in the offspring. **THE SYSTEMIC EXPOSURE (AUC<sub>0-24 hr</sub>) IN RATS AT THIS DOSE WAS LESS THAN THAT IN HUMAN PSORIASIS PATIENTS (0.7 TIMES), WHEN EXTRAPOLATED FOR TREATMENT OF 20% OF BODY SURFACE AREA.** Although there are no adequate and well-controlled studies in pregnant women, TAZORAC™ is contraindicated in women who are or may become pregnant. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, treatment should be discontinued and the patient apprised of the potential hazard to the fetus. Women of child-bearing potential should be warned of the potential risk and use adequate birth-control measures when TAZORAC™ is used. The possibility that a woman of childbearing potential is pregnant at the time of institution of therapy should be considered.

TAZORAC™ is contraindicated in individuals who have shown hypersensitivity to any of its components.

#### **WARNINGS:**

Pregnancy Category X. See "CONTRAINDICATIONS" section. Women of child-bearing potential should use adequate birth-control measures when TAZORAC™ is used. The possibility that a woman of childbearing potential is pregnant at the time of institution of therapy should be considered.

Retinoids should not be used on eczematous skin, as they may cause severe irritation.

Because of heightened burning susceptibility, exposure to sunlight (including sunlamps) should be avoided or minimized during use of TAZORAC™. Patients must be warned to use sunscreens (minimum SPF of 15) and protective clothing when using TAZORAC™. Patients with sunburn should be advised not to use TAZORAC™ until fully recovered. Patients who may have considerable sun exposure due to their occupation and those patients with inherent sensitivity to sunlight should exercise particular caution when using TAZORAC™ and assure that the precautions outlined in the Information for Patients subsection are observed.

TAZORAC™ should not be administered if the patient is also taking drugs known to be photosensitizers (e.g., thiazides, tetracyclines, fluoroquinolones, phenothiazines, sulfonamides) because of the possibility of augmented phototoxicity.

The safety of use over more than 20% of body surface area has not been established in psoriasis or acne.

#### **PRECAUTIONS:**

**General:** TAZORACT™ should only be applied to the affected areas. For external use only. Avoid contact with eyes, eyelids, and mouth. If contact with eyes occurs, rinse thoroughly with water.

If pruritus, burning, skin redness or peeling are excessive, the medication should be discontinued until the integrity of the skin is restored.

TAZORAC™, as a member of the retinoid class, may be teratogenic and/or fetotoxic.

TAZORAC™ should only be applied before retiring at night.

Weather extremes, such as wind or cold, may be more irritating to patients using TAZORAC™.

*The safety of use over more than 20% of body surface area has not been established.*

**Information for Patients:** See attached Patient Package Insert.

**Drug Interactions:** Concomitant dermatologic medications and cosmetics that have a strong drying effect should be avoided. It is also advisable to "rest" a patient's skin until the effects of such preparations subside before use of TAZORAC™ is begun.

**Carcinogenesis, mutagenesis, impairment of fertility:** Long-term studies of tazarotene following oral administration of 0.025, 0.050 and 0.125 mg/kg/day to rats showed no indications of increased carcinogenic risks. However, in other rat studies, oral doses twice that of the highest dose in the rat carcinogenicity study produced an  $AUC_{0-24hr}$  that was less (0.7 times) than that in topically treated psoriatic patients extrapolated for treatment of 20% of body surface area. In evaluation of photocarcinogenicity, median time to onset of tumors was decreased and the number of tumors increased in hairless mice following chronic topical dosing with intercurrent exposure to ultraviolet radiation at tazarotene concentrations of 0.001%, 0.005%, and 0.01% for up to 40 weeks.

Tazarotene was found to be non-mutagenic in the Ames assay and did not produce structural chromosomal aberrations in a human lymphocyte assay. Tazarotene was also non-mutagenic in the CHO/HPRT mammalian cell forward gene mutation assay and was non-clastogenic in the *in vivo* mouse micronucleus test.

No impairment of fertility occurred in rats when male animals were treated for 70 days prior to mating and female animals were treated for 14 days prior to mating and continuing through gestation and lactation with topical doses of TAZORAC™ Gel of up to 0.125 mg/kg/day (0.738 mg/m²/day).

Reproductive capabilities of F1 animals, including F2 survival and development, were not affected by topical administration of TAZORAC™ Gel to female F0 parental rats from gestation day 16 through lactation day 20 at the maximum tolerated dose of 0.125 mg/kg/day (0.738 mg/m²/day).

**Pregnancy: Pregnancy Category X.** See "CONTRAINDICATIONS" section. Women of child-bearing potential should use adequate birth-control measures when TAZORAC™ is used. The possibility that a woman of childbearing potential is pregnant at the time of institution of therapy should be considered.

**Nursing mothers:** After single topical doses of <sup>14</sup>C-tazarotene to the skin of lactating rats, secretion of radioactivity was detected in milk, suggesting that there would be transfer of drug-related material to the offspring via milk. It is not known whether this drug is excreted in human milk. Caution should be exercised when tazarotene is administered to a nursing woman.

**Pediatric Use:** The safety and efficacy of tazarotene have not been established in pediatric patients under the age of 12 years.

#### **ADVERSE REACTIONS:**

The most frequent adverse reactions reported during clinical trials with TAZORAC™ included:

**Psoriasis:**

The following Table shows the incidence of adverse reactions in two large vehicle-controlled clinical studies in which tazarotene 0.1% and 0.05% gels were applied once daily to psoriasis lesions:

	TAZORAC™, 0.05% Gel (N=219)	TAZORAC™, 0.1% Gel (N=220)	Vehicle Gel (N=221)
Patients with AE	68%	70%	
Patients with treatment-related AE	38%	54%	
Withdrawal due to AE	10%	15%	
Pruritus	21%	27%	12%
Burning/stinging	15%	17%	5%
Erythema	11%	15%	2%
Worsening of psoriasis	8%	13%	8%
Irritation	6%	12%	<1%
Skin Pain	6%	10%	3%
Rash	5%	8%	2%
Desquamation	2%	4%	0
Irritant contact dermatitis	2%	4%	<1%
Skin Inflammation	<1%	3%	3%
Fissuring	2%	1%	1%
Bleeding	<1%	1%	<1%
Dry Skin	2%	1%	1%

AE=adverse events

Daily applications to lesions with TAZORAC™ 0.1% or 0.05% Gel were made for 12 months in a long-term study for psoriasis. The following increase in incidence of adverse reactions has been noted over the fourth to twelfth months as compared to the first 3 months:

	TAZORAC™, 0.05% Gel (N=121)		TAZORAC™, 0.1% Gel (N=122)	
	1st 3 months	4th-12th month	1st 3 months	4th-12th month
Psoriasis worsened	8%	17%	10%	13%
Sun-induced erythema	0.8%	2.5%	0%	4%

**Acne:**

The following Table shows the incidence of adverse reactions in two large vehicle-controlled clinical studies in which tazarotene 0.1% gel was applied once daily to facial acne:

	TAZORAC™, 0.1% Gel (N=289)	Vehicle Gel (N=297)
Patients with AE	59%	38%
Patients with treatment-related AE	47%	15%
Withdrawal due to AE	7%	2%
Desquamation	28%	2%
Burning/stinging	26%	3%
Dry skin	20%	5%
Erythema	18%	0
Pruritus	12%	7%
Irritation	5%	1%
Skin pain	2%	0
Fissuring	1%	0
Localized edema	1%	0
Skin discoloration	1%	0

AE=adverse events

In human dermal safety studies, tazarotene 0.1% and 0.05% gels did not induce contact sensitization, phototoxicity or photoallergy. Cumulative irritancy tests showed that tazarotene might be more irritating than tretinoin when applied topically at the same concentration.

**OVERDOSAGE:**

Excessive topical use of TAZORAC™ may lead to marked redness, peeling, or discomfort (see PRECAUTIONS). Inadvertent oral ingestion of the drug may lead to the same adverse effects as those associated with excessive oral intake of Vitamin A (hypervitaminosis A) or other retinoids. If accidental oral ingestion occurs, the patient should be monitored, and appropriate supportive measures should be administered as necessary.

**DOSAGE AND ADMINISTRATION:**

**General:** Application may cause a transitory feeling of burning or stinging. If irritation is excessive, application should be discontinued.

**For psoriasis.** Apply TAZORAC™ once a day, in the evening, to psoriatic lesions, using enough (2 mg/cm<sup>2</sup>) to cover only the lesion with a thin film. If a bath or shower is taken prior to application, the skin should be dry before applying the gel. If emollients are used, they should be applied and allowed to absorb into the skin before application of TAZORAC™. Because unaffected skin may be more susceptible to irritation, application of tazarotene to these areas should be carefully avoided. TAZORAC™ was investigated for up to 12 months during clinical trials for psoriasis.

**For acne:** Cleanse the face gently. After the skin is dry, apply a thin film of TAZORAC™ (2 mg/cm<sup>2</sup>) once a day, in the evening, to the skin where acne lesions appear. Use enough to cover the entire affected area. TAZORAC™ was investigated for up to 12 weeks during clinical trials for acne.

**HOW SUPPLIED:**

TAZORAC™ (tazarotene) Gel is available in concentrations of 0.1% and 0.05%. It comes in collapsible aluminum tubes, in 10 gm, 30 gm and 100 gm sizes.

	TAZORAC™ Gel 0.05%	TAZORAC™ Gel 0.1%
10 gm	NDC 0023-XXXX-XX	NDC 0023-XXXX-XX
30 gm	NDC 0023-XXXX-XX	NDC 0023-XXXX-XX
100 gm	NDC 0023-XXXX-XX	NDC 0023-XXXX-XX

**NOTE:** TAZORAC™ gel should be stored at 25°C (77°F); excursion permitted to 15-30°C (59-86°F).

**CAUTION:** Federal (U.S.A.) law prohibits dispensing without prescription.

Facts pertinent to product.

ALLERGAN Herbert

Skin Care Division of ALLERGAN, INC.

Irvine, California 92715, U.S.A.

December 1996

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## INFORMATION FOR PATIENTS

**Please read this leaflet carefully before you start to use your medicine. If you have any questions, or are not sure about anything, ask your doctor or pharmacist.**

- The active ingredient in TAZORAC™ is tazarotene.
- TAZORAC™ also contains benzyl alcohol as a preservative and the following inactive ingredients: ascorbic acid, butylated hydroxyanisole, butylated hydroxytoluene, carbomer 934P, edetate disodium, hexylene glycol, purified water, poloxamer 407, polyethylene glycol 400, polysorbate 40, and tromethamine.

## USES

TAZORAC™ 0.05% Gel is used in the treatment of stable plaque psoriasis **ONLY**.

TAZORAC™ 0.1% Gel is used in the treatment of stable plaque psoriasis and mild to moderately severe facial acne.

## BEFORE YOU USE THIS MEDICINE

You should be aware that:

- (a) TAZORAC™ should not be used if you are pregnant, attempting to become pregnant or at high risk of pregnancy. Women of child-bearing potential should use adequate birth-control measures when TAZORAC™ is used.
- (b) TAZORAC™ should be used with caution if you are also using other topical agents with a strong skin drying effect, products with high concentrations of alcohol, astringents, spices or lime, medicated soaps or shampoos, permanent wave solutions, electrolysis, hair depilatories or waxes, or other preparations or processes that might dry or irritate the skin, unless otherwise instructed by your health care practitioner.
- (c) TAZORAC™ should not be used if you have sunburn, eczema or other chronic skin condition(s). TAZORAC™ may cause severe irritation if applied to eczematous skin. Because of heightened burning susceptibility, patients with sunburn should not use TAZORAC™ until fully recovered.
- (d) TAZORAC™ should not be used if you are inherently sensitive to sunlight.
- (e) TAZORAC™ should not be used if you are taking other drugs that increase your sensitivity to sunlight. Inform your physician if you are taking any other medications.
- (f) You should use protective clothing and sunscreens with minimum SPF of 15 during the day when being treated with TAZORAC™. You should avoid direct sun exposure as much

as possible and avoid sunlamps totally while being treated with TAZORAC™. Following discontinuation of TAZORAC™, continued avoidance of the sun and use of a sunscreen with a minimum SPF 15 is recommended.

- (g) If you have considerable sun exposure due to occupation, particular caution as described above should be exercised when using TAZORAC™.
- (h) Weather extremes, such as wind or cold, may be more irritating to patients using TAZORAC™.

#### **BEFORE YOU USE THIS MEDICINE**

Tell your doctor:

- (a) if you are pregnant or are considering becoming pregnant.
- (b) if you are breast-feeding.
- (c) if you are allergic to any ingredients in this medicine.
- (d) if you are already using other products that make your skin dry.
- (e) if you have a skin condition called eczema.
- (f) if you will be having excessive sun exposure.
- (g) if you are taking vitamin A supplements.

#### **HOW TO USE THIS PRODUCT:**

- Read the directions on your prescription label carefully. Ask your doctor or pharmacist to explain anything that you do not understand.
- If you become pregnant while using TAZORAC™, you should immediately discontinue its use and contact your doctor.
- If you use a cream or lotion to soften or lubricate your skin, apply it to your skin and allow it to absorb completely before application of TAZORAC™.
- After applying TAZORAC™, some people notice a feeling of itching, burning or stinging. This feeling may occur less often as your skin gets used to the medication. Discontinue use of TAZORAC™ and consult your health care provider if sensitivity or increased chemical irritation occurs.
- Do not cover treatment areas with dressings or bandages.
- Never use more TAZORAC™ than instructed and never use it more often than instructed, as application of larger amounts of medication than recommended will not lead to more rapid or better results, and marked redness, peeling, or discomfort may occur.
- Wash your hands after applying the medication unless you are treating your hands for psoriasis. If the gel accidentally gets on areas you do not need to treat, wash it off.
- If TAZORAC™ comes in contact with your eyes, wash your eyes with large amounts of cool water, and contact a doctor if eye irritation persists.

#### **MISSED DOSES:**

- If you forget or miss a dose of TAZORAC™, do not try to "make it up." Return to your normal application schedule as soon as you can.

#### **INSTRUCTIONS SPECIFIC TO TREATMENT OF PSORIASIS:**

- If you bathe or shower before using TAZORAC™, be sure the skin is dry before application. Apply a thin film of the gel to your psoriasis lesions once a day before going to bed.
- Carefully avoid application to apparently unininvolved skin. TAZORAC™ may be more irritating to non-lesional skin.
- If you need to treat your hands, avoid contact with your eyes.
- Contact your doctor if your psoriasis becomes worse.

#### **INSTRUCTIONS SPECIFIC TO TREATMENT OF ACNE:**

- Gently clean and dry your face before using TAZORAC™. Apply TAZORAC™ once a day, before

going to bed, to entire areas of the face where you have acne lesions. Use enough gel to cover the entire affected area with a thin film.

Follow your doctor's directions for other routine skin care and the use of make-up. Talk to your doctor about the use of sunscreens and cosmetics, especially those that dry your skin.

- Usually, your acne will begin to improve in about 4 weeks. Continue to use TAZORAC™ for up to 12 weeks as directed by your doctor.
- Contact your doctor if your acne becomes worse.

**WARNINGS:**

TAZORAC™ should not be used if you are pregnant, attempting to become pregnant or at high risk of pregnancy. Women of child-bearing potential should use adequate birth-control measures when TAZORAC™ is used.

If TAZORAC™ is swallowed by accident, contact your doctor or a poison control center.

Do not use TAZORAC™ after the expiration date found on the tube.

This medicine is for your use only. It can only be prescribed by a doctor. Never give it to anyone else. It may harm them even if their skin problem appears to be the same as yours.

Retinoids should not be used on eczematous skin, as they may cause severe irritation. Because of heightened burning susceptibility, exposure to sunlight (including sunlamps) should be avoided or minimized during use of TAZORAC™. You should use sunscreens (minimum SPF of 15) and protective clothing when using TAZORAC™. Do not use TAZORAC™ until fully recovered. If you have considerable sun exposure due to occupation or if you have inherent sensitivity to sunlight, you should exercise particular caution when using TAZORAC™ and assure that the precautions outlined above are observed.

Do not use TAZORAC™ if you are also taking drugs known to be photosensitizers (e.g., thiazides, tetracyclines, fluoroquinolones, phenothiazines, sulfonamides) because of the possibility of augmented phototoxicity.

*The safety of use over more than 20% of body surface area has not been established in psoriasis or acne.*

**Instructions for use and Handling:** Keep tube tightly closed when not in use. Store it in a safe place where children cannot reach it. TAZORAC™ Gel should be stored at 25 °C (77 °F); excursion permitted to 15 - 30 °C (59-86 °F).

**If you have questions about TAZORAC™ Gel:** You may contact Allergan Herbert by calling 800-433-8871.

**If you have questions about psoriasis:** Information is available from The National Psoriasis Foundation:  
ADDRESS: PHONE NUMBER.

**ALLERGAN Herbert**

Skin Care Division of Allergan, Inc.  
Irvine, California 92713, U.S.A.  
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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

NDA 20-600

Food and Drug Administration  
Rockville MD 20857

Allergan, Inc.

Attention: Trudy A. Rumbaugh, M.D.  
Director, Global Regulatory Affairs, Retinoids  
2525 Dupont Drive -  
P.O. Box 19534  
Irvine, CA 92713-9534

JUN 6 1996

Dear Dr. Rumbaugh:

Please refer to your June 16, 1995, New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for tazarotene gel, 0.05% and 0.1%.

We acknowledge receipt of your communications dated June 22, 28 (two) and 30, July 7, 10 and 26, August 11, September 21 and 22, October 17 and 30, and December 11, 1995; and January 9, February 5, 26 and 27, March 8, 18, 19, and 27, and April 25, 1996.

This new drug application provides for the treatment of acne vulgaris and plaque psoriasis.

We have completed our review of this application and find the information presented is inadequate, and the application is not approvable under section 505(d) of the Act and 21 CFR 314.125(b).

The deficiencies may be summarized as follows:

Chemistry, Manufacturing, and Controls Issues

1. With regard to the description and characterization of the drug substance the information presented on page 3-029 is not sufficient to support the absence of polymorphs. Please submit full details of the study using hot stage microscopy that concludes that no polymorphs were found. Furthermore, it is our suggestion that studies which use Fourier transform infrared spectroscopy (FTIR), differential scanning calorimetry (DSC), or thermal gravimetric analysis (TGA) in combination with hot stage microscopy would be preferred for demonstrating the presence or absence of polymorphism in AGN 190168.

2. Please provide the full address of the Allergan testing site that performs final release and stability testing of tazarotene bulk drug substance for Cambridge Chemical and Torcan Chemical.
3. With regard to the synthesis/method of manufacture of the bulk drug substance manufactured at Torcan:
  - A. The list of components provided by Torcan for the manufacture of tazarotene bulk drug substance (BDS) is incomplete. A list of all components used in steps one through seven should be submitted for our evaluation (i.e., 3-methyl-2-buten-1-ol, thiophenol, sodium hydroxide, 50%, and phosphorous tribromide). When compiling a list of components, please include the quality or grade of the inactive component (i.e., USP, ACS, etc.).
  - B. Please provide Certificates of Analysis of starting materials used by Torcan for 3-methyl-2-buten-1-ol, trimethylsilyl acetylene, and ethyl 6-ethoxynicotinate.
  - C. Please specify the identity testing that is performed for 3-methyl-2-buten-1-ol. In addition, please include the acceptance specifications for this starting material.
  - D. Please provide the procedure used for the purification of ethyl 6-chloronicotinate at the Torcan facility. Please include GC and HPLC chromatograms along with the identification of impurities such as B922, B921, and A087.
  - E. Please provide information to demonstrate that ethyl 6-chloronicotinate is a commercially available starting material used at both Torcan and Cambridge. If it is not, please provide full details of the chemistry, manufacture, and control of this intermediate from commercially available starting material.
  - F. The specification for the intermediate AGN 190906, B658, by GC is not less than (NLT) 95% w/w. Please identify any impurities that form as byproducts or degradants, up to 3%.

- G. Please identify the in-process tests used to detect the formation of the intermediate product, phenyl(3-methyl butyl-2-enyl)sulfide, in step 1.
  - H. Please identify any impurities that result from byproduct formation or degradation in the preparation of AGN 192050. In general, we suggest that an impurity profile for each step of the Torcan synthesis of tazarotene BDS be submitted.
  - I. Please state whether there are any other other identifiable peaks in the HPLC for AGN 192049 (B751). In addition, please list other impurities besides the starting material that may be present at less than 0.5% with respect to B751.
  - J. The proposal to increase the batch size of step 3 from a 30 kg reaction scale to a 160 kg reaction scale did not address "scale-up" procedures for the remaining steps. Please provide the rationale justifying the omission of the "scale-up" procedures.
  - K. We have concerns about the capability of Torcan to scale up the synthesis. We recommend that a "scaled-up" batch be synthesized and analyzed and the data submitted for our evaluation.
  - L. In general, the broadness in "product" yield at each synthetic step in the manufacture of AGN 190168 at Torcan may imply that the consistency in control of the chemical reaction is still being evaluated. Please submit a tabular summary of reaction yields at each of the 7 steps for at least 3 or more lots of AGN 190168 for our evaluation.
  - M. The in-process control step for B660H1 introduces an unidentified standard B661. Please identify the standard used. In addition, please provide the rationale explaining why the the retention times for crude tazarotene (RT 8.68 min), B662, and purified tazarotene (Rt 5.0 min), B928, are different.
4. With regard to the bulk drug substance manufactured at the Cambridge facility:

- A. Please provide the numerical release specifications for purchased and purified 1-bromo-3-methyl-2-butene.

B. Please identify the impurities found in the GC chromatogram on page 6-271 for the synthesis of CCI002.

C. Please provide tables for components and equipment for steps 1 and 2, the formation of AGN 190906, CCI002.

D. The tests for heavy metals, copper and palladium, which are used in steps 4 and 6 of the tazarotene manufacturing process have been omitted by the Cambridge facility. A commitment to add this control, with a specification of not more than 20 ppm, to the release controls at the Cambridge facility should be submitted.

5. With regard to the regulatory specifications/analytical method:

A. From the data reported, the melting point of tazarotene may not be a crucial release parameter when all the other supportive tests are considered. The change in the melting range specifications at the contract manufacturers and at the testing facility for release is not consistent. Efforts to abide by USP testing as stated in section 741 have resulted in the accommodation of the data to fit the specifications. We recommend that either you return to testing with differential scanning calorimetry (DSC) or that you formally withdraw this release control due to melting range variability.

B. Data from Torcan for the HPLC weight assay has been reported in appendix 3.7.4D. Please provide the rationale for the omission of the information on the HPLC weight assay of tazarotene and related substances manufactured at the Cambridge facility.

C. Prior to evaluating the method validation of the HPLC weight percent assay procedure for AGN 190168 BDS and related substances, the following information is requested:

  - The accuracy of the method for tazarotene and its impurities.
  - Raw data for linearity and precision.

6. With regard to the container/closure system for storage:

In addition to the HPDE container, a tin plated steel can secondary container has been used at the Cambridge facility in stability studies for the tazarotene. This information was not presented as an additional secondary storage container in section 3.2.3.15. Please clarify if it will be an alternative secondary container for the drug substance at both the Cambridge and Torcan facilities.

7. With regard to the manufacturer of the drug product:

A. The testing facility for release and stability testing of the drug product at Allergan in Irvine, California, was not reported under manufacturing facilities. Please submit the full address and specific function of this facility for our review and evaluation.

B. If post-approval stability testing of tazarotene gel will be performed by Allergan (Ireland), please provide full details for drug product testing of the qualification lots.

C. Please submit a copy of an executed batch record for a primary stability batch.

8. With regard to the regulatory specifications/methods:

We suggest that additional test parameters for the in-process control of the drug product be reported in table 3.3.6.2-1 on page 3-182. Please submit in-process controls for tazarotene, related substance AGN 190299, and related substance AGN 190832.

9. With regard to the drug product stability:

A. Please clarify what batches of drug product, representative of active from both Torcan and Cambridge, are assigned as qualification batches.

- B. The inhomogeneity effect at 25°C/60%RH represents a significant problem in maintaining tazarotene gel stability for both formulations (8606X and 8607X-A) within the proposed specifications. It is our understanding that the proposed commercial size batch will be 1300 kg, while your previous stability studies have been performed on 90 kg batches. At least 2 batches manufactured at a minimum of one tenth (130 kg) the commercial size, combined with the 90 kg batches, are required to establish the expiration dating period.
- C. Assay values for tazarotene gel stored at 25°C/60%RH were found to be out of specification. Only selected data for the degradant profile were recorded (i.e., Table 123, page 9-340). No data for the other stability tests were recorded. Please submit all drug product stability data so that we may examine the inhomogeneity effect on the other test parameters.

### Biopharmaceutics Issue

The stability of tazarotene and metabolite in biological samples should be tested at the concentration range similar to that found in the pharmacokinetic studies and clinical trials.

### Microbiology Issues

1. Regarding the Preservative Effectiveness Testing (PET) and Microbial Limits Testing (MLT):
- A. Please provide the methods used for both the PET and MLT tests. If the tests are USP tests, this should be stated.
- B. Please provide numerical test results from the PET tests performed which demonstrate the effectiveness of the preservative system at the lowest concentration specification for the benzyl alcohol.
- C. Please provide the acceptance specifications for the Microbial Limits Tests. Specifications should be established for total aerobic count, total yeasts and molds, and absence of indicator pathogens.

2. Please describe any in-process programs and controls that will be used to control microbial quality of the bulk drug substance.

**Clinical Issue**

Differences in the formulations used in the pivotal trials were noted. As these may impact on the approvability of the drug product, please provide the qualitative and quantitative characteristics of the ingredients.

**Pharmacology Issues**

1. The following items are required to allow us to make a final judgment on the adequacy of the submitted dermal carcinogenicity and oral rodent toxicity studies:
  - A. The dietary data set, including the weight gain and food consumption data, for both studies.
  - B. A code book for the tumorigenicity data.
  - C. Survival and onset data for the tumors.

Please submit all safety information you now have regarding your new drug, in accordance with the requirements of 21 CFR 314.50(d)(5)(vi)(b). Please provide updated information as listed below:

- A. Retabulate all safety data, including results of trials that were still ongoing at the time of NDA submission. The tabulation should take the same form as in your initial submission. Tables comparing adverse reactions at the time the NDA was submitted versus now will certainly facilitate review.
- B. Retabulate drop-outs with new drop-outs identified. Provide discussion where appropriate.
- C. Submit case report forms for each patient who died during a clinical study or who did not complete a study because of an adverse event.
- D. Provide details of any significant changes or findings, if any.

E. Summarize worldwide experience on the safety of this drug.

In addition, please update the new drug application with respect to reports of relevant safety information, including all deaths and any adverse events that led to discontinuation of the drug and any information suggesting a substantial difference in the rate of occurrence of common, but less serious, adverse events. The update should cover all studies worldwide and uses of the drug including:

- A. Those involving indications not being sought in the present submission,
- B. Other dosage forms, and other dose levels, etc.

We reserve comment on the proposed labeling for this drug product until its safety and effectiveness have been established. However, the proposed proprietary name for this drug product, "Zorac<sup>TM</sup>" was judged to be unacceptable by the CDER Labeling and Nomenclature Committee.

We remind you that a satisfactory inspection of your manufacturing facilities for conformance with good manufacturing practices (CGMP) is required before this application may be approved.

Although not the basis of the non-approval action for this application, additional comments and requests for information will be provided to you in a separate communication.

In accordance with the policy described in 21 CFR 314.102(d) of the new drug regulations, you may request an informal conference with the members of the Division of Dermatologic and Dental Drug Products to discuss in detail the issues associated with this application. The meeting is to be requested at least fifteen days in advance.

Within 10 days after the date of this letter, you are required to amend the application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.120. In the absence of any such action, FDA may proceed to withdraw the application. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

Should you have any questions regarding this application, please contact:

Frank Cross, Jr., MA, LCDR  
Project Manager  
(301) 827-2020

Sincerely yours,

*M. Weintraub*

Michael Weintraub, M.D.  
Director *XAV 105*  
Office of Drug Evaluation V  
Center for Drug Evaluation and Research

The reviewers for this application consisted of:

Jonathan K. Wilkin, M.D., Division Director, DODDDP, HFD-540  
Linda Katz, M.D., Deputy Division Director, DODDDP, HFD-540  
Hon Sum Ko, M.D., Medical Officer, DODDDP, HFD-540  
R. Srinivasan, Ph.D., Biostatistics Team Leader, DOBIV, HFD-725  
Steve Thomson, Ph.D., Biostatistician, DOBIV, HFD-725  
Abby Jacobs, Ph.D., Pharmacology/Toxicology Team Leader, DODDDP, HFD-540  
Hilary Sheevers, Ph.D., Toxicologist, DODDDP, HFD-540  
Amy Nostrandt, D.V.M., Ph.D., Toxicologist, DODDDP, HFD-540  
Eric Sheinin, Ph.D., Director, DNDCIII, HFD-830  
Wilson DeCamp, Ph.D., Chemistry Team Leader, DNDCIII, HFD-540  
Sydney Gilman, Ph.D., Chemist, DNDCII, HFD-160  
Dennis Bashaw, Ph.D., Biopharmaceutics Team Leader, DPEIII, HFD-880  
Frank Pelsor, Ph.D., Biopharmaceutics Team Leader, DPEIII, HFD-880  
Sue-Chih Lee, Ph.D., Biopharmaceuticist, DPEIII, HFD-880  
Peter Cooney, Ph.D., Microbiology Supervisor, ONDC, HFD-160  
Patricia Hughes, Ph.D., Microbiologist, ONDC, HFD-160  
Maria Rossana R. Cook, M.B.A., Supervisory Project Manager, DODDDP, HFD-540  
Frank Cross, MA, LCDR, Regulatory Management Officer, DODDDP, HFD-540



## DEPARTMENT OF HEALTH &amp; HUMAN SERVICES

Public Health Service

Food and Drug Administration  
Rockville MD 20857

NDA 20-600

Allergan, Inc.  
Attention: Trudy A. Rumbaugh, M.D.  
Director, Global Regulatory Affairs, Retinoids  
2525 Dupont Drive  
P.O. Box 19534  
Irvine, CA 92713-9534

JUN 13 1997

Dear Dr. Rumbaugh:

Please refer to your June 16, 1995, New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Tazorac™ (tazarotene topical gel), 0.05% and 0.1%.

Please refer to our Not Approvable letter dated June 6, 1996, and our Approvable Letter dated December 30, 1996.

We acknowledge receipt of your amendments and correspondence dated January 2 and 17, February 5 and 25, March 17, 18, and 28, April 11, and May 28, 1997. The User Fee Goal date for this application is July 21, 1997.

This new drug application provides for the topical treatment of patients with stable plaque psoriasis of up to 20% body surface area involvement and topical treatment of patients with facial acne vulgaris of mild to moderate severity.

We have completed the review of this application, including the submitted draft labeling, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the enclosed final version of the labeling. Accordingly, the application is approved effective upon the date of this letter.

The final printed labeling (FPL) must be identical to the attached revised labeling. The attached revised labeling was stated to be acceptable to you in the facsimile of your letter dated June 10, 1997. Marketing the product with FPL that is not identical to this draft labeling may render the product misbranded and an unapproved new drug.

Please submit twenty copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount ten of the copies on heavy weight paper or similar

NDA 20-600

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material. For administrative purposes this submission should be designated "FINAL PRINTED LABELING" for approved NDA 20-600. Approval of this submission by FDA is not required before the labeling is used.

Should additional information relating to the safety and effectiveness of the drug become available, revision of that labeling may be required.

We remind you of your Phase 4 commitments specified in your submissions dated January 17, March 17, 1997, and in the facsimiles of your letters dated June 11, 1997. These commitments, along with any completion dates agreed upon, are listed below:

1. A follow-up on the incidence of photosensitivity associated with long term use of tazarotene.
2. A description of the scale up procedures for the bulk drug substance at the Torcan manufacturing facility. Details of this commitment will be submitted to the Agency 30 days after approval of this NDA. The following information should be included:

Procedural details for the manufacture of 35 to 60 kg of bulk drug substance at the Torcan Facility.

A comparison of the new drug substance under controlled room temperature and accelerated storage at release and at three months to data from a previous lot. This information should be submitted within 120 days post approval of this NDA. In addition, since this drug substance will be used in the manufacture of Tazorac™ prior to our request for lot comparisons, you will remove from the commercial manufacture any lot failing to meet acceptance criteria.

3. A drug-drug interaction study between tazarotene and oral contraceptive agents in female psoriatic patients to demonstrate contraceptive efficacy. Patients participating in the study should have large surface areas of psoriatic skin consistent with the proposed labeling. The study design for topical administration of tazarotene should be similar to that of study R168-153-8606. This study should provide the additional data for comparisons between genders. Both combination and single-entity oral contraceptives (i.e., minipills) should be studied. Study protocol should be submitted to the Agency for review within 60 days post approval. The study should be initiated within 6 months of approval.

Clinical protocols, data, and final reports should be submitted to your IND for this product and a copy of the cover letter sent to this NDA. Should an IND not be required to meet your Phase 4 commitments, please submit protocol, data, and final reports to this NDA as correspondences. In addition, we request under 21 CFR 314.81(b)(2)(vii) that you include in your annual report to

NDA 20-600

Page 3

this application, a status summary of each commitment. The status summary should include the number of patients entered in each study, expected completion dates, and any changes in plans since the last annual report. For administrative purposes, all submissions, including labeling supplements, relating to these Phase 4 commitments must be clearly designated "Phase 4 Commitments."

In addition, please submit three copies of the introductory promotional material that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print. Please submit one copy to the Division of Dermatologic and Dental Drug Products and two copies of both the promotional material and the package insert directly to:

Food and Drug Administration  
Division of Drug Marketing, Advertising and Communications,  
HFD-40  
5600 Fishers Lane  
Rockville, Maryland 20857

Validation of the regulatory methods has not been completed. At the present time, it is the policy of the Center not to withhold approval because the methods are being validated. Nevertheless, we expect your continued cooperation to resolve any problems that may be identified.

Please submit one market package of the drug when it is available.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

NDA 20-600  
Page 4

If you have any questions, please contact:

Frank H. Cross, Jr., M.A., LCDR  
Regulatory Management Officer  
(301) 827-2020

Sincerely yours,

*M Weintraub 6/13/97*

Michael Weintraub, M.D.  
Director  
Office of Drug Evaluation V  
Center for Drug Evaluation and Research

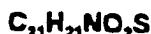
Enclosure

**TAZORAC™**  **ALLERGAN**  
**(tazarotene topical gel) 0.05%**  
**(tazarotene topical gel) 0.1%**

**FOR DERMATOLOGIC USE ONLY**  
**NOT FOR OPHTHALMIC USE**

**DESCRIPTION:**

TAZORAC™ is a translucent, aqueous gel and contains the compound tazarotene, a member of the acetylenic class of retinoids. It is for topical dermatologic use only. The active ingredient is represented by the following structural formula:



Molecular Weight: 351.46

Chemical Name: ethyl 6-[2-(4,4-dimethylthiochroman-6-yl)-ethynyl] nicotinate

**Contains:**

**Active:** Tazarotene..... 0.05% or 0.1% (w/w)

**Preservative:** Benzyl alcohol..... 1.0% (w/w)

**Inactives:** Ascorbic acid, butylated hydroxyanisole, butylated hydroxytoluene, carbomer 934P, edetate disodium, hexylene glycol, purified water, poloxamer 407, polyethylene glycol 400, polysorbate 40, and tromethamine.

**CLINICAL PHARMACOLOGY:**

Tazarotene is a retinoid prodrug which is converted to its active form, the cognate carboxylic acid of tazarotene (AGN 190299), by rapid deesterification in most biological systems. AGN 190299 binds to all three members of the retinoic acid receptor (RAR) family: RAR $\alpha$ , RAR $\beta$ , and RAR $\gamma$ , but shows relative selectivity for RAR $\beta$ , and RAR $\gamma$  and may modify gene expression. The clinical significance of these findings is unknown.

**Psoriasis:** The mechanism of tazarotene action in psoriasis is not defined. Topical tazarotene blocks induction of mouse epidermal ornithine decarboxylase (ODC) activity, which is associated with cell proliferation and hyperplasia. In cell culture and *in vitro* models of skin, tazarotene suppresses expression of MRP8, a marker of inflammation present in the epidermis of psoriasis subjects at high levels. In human keratinocyte cultures, it inhibits cornified envelope formation, whose build-up is an element of the psoriatic scale. The clinical significance of these findings is unknown.

**Acne:** The mechanism of tazarotene action in acne is not defined. Tazarotene inhibited comedocyte accumulation in rhino mouse skin and cross-linked envelope formation in cultured human keratinocytes. The clinical significance of these findings is unknown.

**Pharmacokinetics:**

Following topical application, tazarotene undergoes esterase hydrolysis to form its active metabolite, AGN 190299. Little parent compound could be detected in the plasma. AGN 190299 was highly bound to plasma proteins (>99%). Tazarotene and AGN 190299 were metabolized to sulfoxides, sulfones and other polar metabolites which were eliminated through urinary and fecal pathways. The half-life of AGN 190299 following topical application of tazarotene was similar in normal and psoriatic subjects, approximately 18 hours.

The human *in vivo* studies described below were conducted with tazarotene gel applied topically at approximately 2 mg/cm<sup>2</sup> and left on the skin for 10 to 12 hours. Both the peak plasma concentration

(Cmax) and area under the plasma concentration time curve (AUC) refer to the active metabolite only.

Two single, topical dose studies were conducted using <sup>14</sup>C-tazarotene gel. Systemic absorption, as determined from radioactivity in the excreta, was less than 1% of the applied dose (without occlusion) in six psoriatic patients and approximately 5% of the applied dose (under occlusion) in six healthy subjects. One non-radiolabeled single-dose study comparing the 0.05% gel to the 0.1% gel in healthy subjects indicated that the Cmax and AUC were 40% higher for the 0.1% gel.

After 7 days of topical dosing with measured doses of tazarotene 0.1% gel on 20% of the total body surface without occlusion in 24 healthy subjects, the Cmax was  $0.72 \pm 0.58$  ng/mL (mean  $\pm$  SD) occurring 9 hours after the last dose, and the  $AUC_{0-24h}$  was  $10.1 \pm 7.2$  ng.hr/mL. Systemic absorption was  $0.91 \pm 0.67\%$  of the applied dose.

In a 14-day study in five psoriatic patients, measured doses of tazarotene 0.1% gel were applied daily by nursing staff to involved skin without occlusion (8 to 18% of total body surface area; mean  $\pm$  SD:  $13 \pm 5\%$ ). The Cmax was  $12.0 \pm 7.6$  ng/mL occurring 6 hours after the final dose, and the  $AUC_{0-24h}$  was  $105 \pm 55$  ng.hr/mL. Systemic absorption was  $14.8 \pm 7.6\%$  of the applied dose. Extrapolation of these results to represent dosing on 20% of total body surface yielded estimates of Cmax of  $18.9 \pm 10.6$  ng/mL and  $AUC_{0-24h}$  of  $172 \pm 88$  ng.hr/mL.

An in vitro percutaneous absorption study, using radiolabeled drug and freshly excised human skin or human cadaver skin, indicated that approximately 4 to 5% of the applied dose was in the stratum corneum (tazarotene: AGN190299=5:1) and 2 to 4% was in the viable epidermis-dermis layer (tazarotene: AGN190299=2:1) 24 hours after topical application of the gel.

#### Clinical Studies:

##### Psoriasis:

In two large vehicle-controlled clinical studies, tazarotene 0.1% and 0.05% gels applied once daily for 12 weeks were significantly more effective than vehicle in reducing the severity of the clinical signs of stable plaque psoriasis covering up to 20% of body surface area. In one of the studies, patients were followed up for an additional 12 weeks following cessation of therapy with TAZORAC™. Mean baseline scores and changes from baseline (reductions) after treatment in these two studies are shown in the following Table:

Plaque Elevation, Scaling and Erythema in Two Controlled Clinical Trials for Psoriasis

	TAZORAC™ 0.05% Gel				TAZORAC™ 0.1% Gel				Vehicle Gel			
	Trunk/Arm/ Leg lesions		Knee/Elbow lesions		Trunk/Arm/ Leg lesions		Knee/Elbow lesions		Trunk/Arm/ Leg lesions		Knee/Elbow lesions	
	N=108	N=111	N=108	N=111	N=108	N=112	N=108	N=112	N=108	N=113	N=108	N=113
Plaque elevation	B*	2.5	2.6	2.6	2.6	2.5	2.6	2.6	2.4	2.6	2.6	2.6
	C-12*	-1.4	-1.3	-1.3	-1.1	-1.4	-1.4	-1.5	-1.3	-0.8	-0.7	-0.7
	C-24*	-1.2		-1.1		-1.1		-1.0		-0.9		-0.6
Scaling	B*	2.4	2.5	2.5	2.6	2.4	2.6	2.5	2.7	2.4	2.6	2.5
	C-12*	-1.1	-1.1	-1.1	-0.9	-1.3	-1.3	-1.2	-1.2	-0.7	-0.7	-0.6
	C-24*	-0.9		-0.8		-1.0		-0.8		-0.8		-0.7
Erythema	B*	2.4	2.7	2.2	2.5	2.4	2.8	2.3	2.5	2.3	2.7	2.2
	C-12*	-1.0	-0.8	-0.9	-0.8	-1.0	-1.1	-1.0	-0.8	-0.6	-0.5	-0.5
	C-24*	-1.1		-0.7		-0.9		-0.8		-0.7		-0.6

Plaque elevation, scaling and erythema scored on a 0-4 scale with 0=none, 1=mild, 2=moderate, 3=severe and 4=very severe

\*B=Mean Baseline Severity C-12=Mean Change from Baseline at end of 12 weeks of therapy

C-24=Mean Change from Baseline at week 24 (12 weeks after the end of therapy).

Global improvement over baseline at the end of 12 weeks of treatment in these two studies is shown in the following Table:

	TAZORAC™, 0.05% Gel		TAZORAC™, 0.1% Gel		Vehicle Gel	
	N=81	N=93	N=79	N=69	N=84	N=91
100% improvement	2 (2%)	1 (1%)	0	0	1 (1%)	0
≥75% improvement	23 (28%)	17 (18%)	30 (38%)	17 (25%)	10 (12%)	9 (10%)
≥50% improvement	42 (52%)	39 (42%)	51 (65%)	36 (52%)	28 (33%)	21 (23%)
1-49% improvement	21 (26%)	32 (34%)	18 (23%)	23 (33%)	27 (32%)	32 (35%)
No change or worse	18 (22%)	22 (24%)	10 (13%)	10 (14%)	29 (35%)	38 (42%)

The 0.1% gel was more effective than the 0.05% gel, but the 0.05% gel was associated with less local irritation than the 0.1% gel (see ADVERSE REACTIONS section).

#### Acne:

In two large vehicle-controlled studies, tazarotene 0.1% gel applied once daily was significantly more effective than vehicle in the treatment of facial acne vulgaris of mild to moderate severity. Percent reductions in lesion counts after treatment for 12 weeks in these two studies are shown in the following Table:

#### Reduction in Lesion Counts after Twelve Weeks of Treatment in Two Controlled Clinical Trials for Acne

	TAZORAC™ 0.1% Gel		Vehicle Gel	
	N=150	N=149	N=148	N=149
Noninflammatory lesions	55%	43%	35%	27%
Inflammatory lesions	42%	47%	30%	28%
Total lesions	52%	45%	33%	27%

Global improvement over baseline at the end of 12 weeks of treatment in these two studies is shown in the following Table:

	TAZORAC™ 0.1% Gel		Vehicle Gel	
	N=105	N=117	N=117	N=110
100% improvement	1 (1%)	0	0	0
>75% improvement	40 (38%)	21 (18%)	23 (20%)	11 (10%)
≥50% improvement	71 (68%)	56 (48%)	47 (40%)	32 (29%)
1-49% improvement	23 (22%)	49 (42%)	48 (41%)	46 (42%)
No change or worse	11 (10%)	12 (10%)	22 (19%)	32 (29%)

#### INDICATIONS AND USAGE:

TAZORAC™ (tazarotene topical gel) 0.05% and 0.1% are indicated for the topical treatment of patients with stable plaque psoriasis of up to 20% body surface area involvement.

TAZORAC™ (tazarotene topical gel) 0.1% is also indicated for the topical treatment of patients with facial acne vulgaris of mild to moderate severity.

The efficacy of TAZORAC™ in the treatment of acne previously treated with other retinoids or resistant to oral antibiotics has not been established.

**CONTRAINDICATIONS:**

Retinoids may cause fetal harm when administered to a pregnant woman.

In rats, tazarotene 0.05%, administered topically during gestation days 6 through 17 at 0.25 mg/kg/day (1.5 mg/m<sup>2</sup>/day) resulted in reduced fetal body weights and reduced skeletal ossification. Rabbits dosed topically with 0.25 mg/kg/day (2.75 mg/m<sup>2</sup> total body surface area/day) tazarotene during gestation days 6 through 18 were noted with single incidences of known retinoid malformations, including spina bifida, hydrocephaly, and heart anomalies. As with other retinoids, when tazarotene was given orally to experimental animals, developmental delays were seen in rats, and teratogenic effects and post-implantation fetal loss were seen in rats and rabbits at doses producing 0.7 and 13 times, respectively, the systemic exposure (AUC<sub>0-24hr</sub>) in human psoriasis patients, when extrapolated for topical treatment of 20% of body surface area. **THUS, SYSTEMIC EXPOSURE IN TOPICALLY TREATED PSORIASIS PATIENTS (FOR USE ON UP TO 20% OF BODY SURFACE AREA) COULD BE IN THE SAME ORDER OF MAGNITUDE AS IN THESE ORALLY TREATED ANIMALS.**

Systemic exposure anticipated in the treatment of facial acne may be less, due to a more limited area of application.

Six women inadvertently exposed to TAZORAC™ during pregnancy in clinical trials have subsequently delivered healthy babies. As the exact timing and extent of exposure in relation to the gestation time are not certain, the significance of these findings is not known.

TAZORAC™ is contraindicated in women who are or may become pregnant. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, treatment should be discontinued and the patient apprised of the potential hazard to the fetus. Women of child-bearing potential should be warned of the potential risk and use adequate birth-control measures when TAZORAC™ is used. The possibility that a woman of childbearing potential is pregnant at the time of institution of therapy should be considered. A negative result for pregnancy test having a sensitivity down to at least 50 mIU/ml for human chorionic gonadotropin (hCG) should be obtained within 2 weeks prior to TAZORAC™ therapy, which should begin during a normal menstrual period.

TAZORAC™ is contraindicated in individuals who have shown hypersensitivity to any of its components.

**WARNINGS:**

Pregnancy Category X. See CONTRAINDICATIONS section. Women of child-bearing potential should be warned of the potential risk and use adequate birth-control measures when TAZORAC™ is used. The possibility that a woman of childbearing potential is pregnant at the time of institution of therapy should be considered. A negative result for pregnancy test having a sensitivity down to at least 50 mIU/ml for hCG should be obtained within 2 weeks prior to TAZORAC™ therapy, which should begin during a normal menstrual period.

**PRECAUTIONS:**

**General:** TAZORAC™ should only be applied to the affected areas. For external use only. Avoid contact with eyes, eyelids, and mouth. If contact with eyes occurs, rinse thoroughly with water. The safety of use over more than 20% of body surface area has not been established in psoriasis or acne..

Retinoids should not be used on eczematous skin, as they may cause severe irritation.

Because of heightened burning susceptibility, exposure to sunlight (including sunlamps) should be avoided unless deemed medically necessary, and in such cases, exposure should be minimized during the use of TAZORAC™. Patients must be warned to use sunscreens (minimum SPF of 15) and protective clothing when using TAZORAC™. Patients with sunburn should be advised not to use TAZORAC™ until fully recovered. Patients who may have considerable sun exposure due to their occupation and those patients with inherent sensitivity to sunlight should exercise particular caution when using TAZORAC™ and ensure that the precautions outlined in the Information for Patients subsection are observed.

TAZORAC™ should be administered with caution if the patient is also taking drugs known to be photosensitizers (e.g., thiazides, tetracyclines, fluoroquinolones, phenothiazines, sulfonamides) because of the increased possibility of augmented photosensitivity.

If pruritus, burning, skin redness or peeling is excessive, the medication should be discontinued until the integrity of the skin is restored.

Weather extremes, such as wind or cold, may be more irritating to patients using TAZORAC™.

**Information for Patients:** See attached Patient Package Insert.

**Drug Interactions:** Concomitant dermatologic medications and cosmetics that have a strong drying effect should be avoided. It is also advisable to "rest" a patient's skin until the effects of such preparations subside before use of TAZORAC™ is begun.

**Carcinogenesis, mutagenesis, impairment of fertility:** Long-term studies of tazarotene following oral administration of 0.025, 0.050, and 0.125 mg/kg/day to rats showed no indications of increased carcinogenic risks. However, in other rat studies, oral doses twice that of the highest dose in the rat carcinogenicity study produced an  $AUC_{0-24h}$  that was less (0.7 times) than that in topically treated psoriatic patients extrapolated for treatment of 20% of body surface area. In evaluation of photocarcinogenicity, median time to onset of tumors was decreased and the number of tumors increased in hairless mice following chronic topical dosing with intercurrent exposure to ultraviolet radiation at tazarotene concentrations of 0.001%, 0.005%, and 0.01% for up to 40 weeks.

A long-term topical application study in mice terminated at 88 weeks showed that at dose levels of 0.05, 0.125, 0.25 and 1.0 mg/kg/day (reduced to 0.5 mg/kg/day for males after 41 weeks due to severe dermal irritation) revealed no apparent carcinogenic effects when compared to vehicle control animals; untreated control animals were not completely evaluated. The  $AUC_{0-1hr}$ 's for these doses were 82.7, 137, 183, 136 (males at 1.0/0.5 mg/kg), and 344 ng·hr/ml (females at 1.0 mg/kg), respectively. The mean  $AUC_{0-24h}$  for psoriatic patients was 172 ng·hr/ml, extrapolated for 20% total body surface area.

Tazarotene was found to be non-mutagenic in the Ames assay and did not produce structural chromosomal aberrations in a human lymphocyte assay. Tazarotene was also non-mutagenic in the CHO/HPRT mammalian cell forward gene mutation assay and was non-clastogenic in the *in vivo* mouse micronucleus test.

No impairment of fertility occurred in rats when male animals were treated for 70 days prior to mating and female animals were treated for 14 days prior to mating and continuing through gestation and lactation with topical doses of TAZORAC™ Gel of up to 0.125 mg/kg/day (0.738 mg/m²/day).

Reproductive capabilities of F1 animals, including F2 survival and development, were not affected by topical administration of TAZORAC™ Gel to female F0 parental rats from gestation day 16 through lactation day 20 at the maximum tolerated dose of 0.125 mg/kg/day (0.738 mg/m²/day).

**Pregnancy: Teratogenic Effects: Pregnancy Category X.** See CONTRAINDICATIONS section. Women of child-bearing potential should use adequate birth-control measures when TAZORAC™ is used. The possibility that a woman of childbearing potential is pregnant at the time of institution of therapy should be considered. A negative result for pregnancy test having a sensitivity down to at least 50 mIU/ml for hCG should be obtained within 2 weeks prior to TAZORAC™ therapy, which should begin during a normal menstrual period.

**Nursing mothers:** After single topical doses of <sup>14</sup>C-tazarotene to the skin of lactating rats, secretion of radioactivity was detected in milk, suggesting that there would be transfer of drug-related material to the offspring via milk. It is not known whether this drug is excreted in human milk. Caution should be exercised when tazarotene is administered to a nursing woman.

**Pediatric Use:** The safety and efficacy of tazarotene have not been established in pediatric patients under

the age of 12 years.

#### **ADVERSE REACTIONS:**

##### **Psoriasis:**

The most frequent adverse events reported with TAZORAC™ 0.05% and 0.1% gels were limited to the skin. Those occurring in 10 to 30% of patients, in descending order, included pruritus, burning/stinging, erythema, worsening of psoriasis, irritation, and skin pain. Events occurring in 1 to 10% of patients included rash, desquamation, irritant contact dermatitis, skin inflammation, fissuring, bleeding and dry skin. Increases in "psoriasis worsening" and "sun-induced erythema" were noted in some patients over the 4th to 12th months as compared to the first three months of a 1 year study. In general, the incidence of adverse events with TAZORAC™ 0.05% Gel was 2 to 5% lower than that seen with TAZORAC™ 0.1% Gel.

##### **Acne:**

The most frequent adverse events reported with TAZORAC™ 0.1% gel were limited to the skin. Those events occurring in 10 to 30% of patients, in descending order, included desquamation, burning/stinging, dry skin, erythema and pruritus. Events occurring in 1 to 10% of patients included irritation, skin pain, fissuring, localized edema and skin discoloration.

In human dermal safety studies, tazarotene 0.05% and 0.1% gels did not induce contact sensitization, phototoxicity or photoallergy.

#### **OVERDOSAGE:**

Excessive topical use of TAZORAC™ may lead to marked redness, peeling, or discomfort (see PRECAUTIONS).

TAZORAC™ is not for oral use. Oral ingestion of the drug may lead to the same adverse effects as those associated with excessive oral intake of Vitamin A (hypervitaminosis A) or other retinoids. If oral ingestion occurs, the patient should be monitored, and appropriate supportive measures should be administered as necessary.

#### **DOSAGE AND ADMINISTRATION:**

**General:** Application may cause a transitory feeling of burning or stinging. If irritation is excessive, application should be discontinued.

**For psoriasis:** Apply TAZORAC™ once a day, in the evening, to psoriatic lesions, using enough ( $2 \text{ mg/cm}^2$ ) to cover only the lesion with a thin film to no more than 20% of body surface area. If a bath or shower is taken prior to application, the skin should be dry before applying the gel. Because unaffected skin may be more susceptible to irritation, application of tazarotene to these areas should be carefully avoided. TAZORAC™ was investigated for up to 12 months during clinical trials for psoriasis.

**For acne:** Cleanse the face gently. After the skin is dry, apply a thin film of TAZORAC™ ( $2 \text{ mg/cm}^2$ ) once a day, in the evening, to the skin where acne lesions appear. Use enough to cover the entire affected area. TAZORAC™ was investigated for up to 12 weeks during clinical trials for acne.

#### **HOW SUPPLIED:**

TAZORAC™ (tazarotene topical gel) is available in concentrations of 0.05% and 0.1%. It comes in collapsible aluminum tubes, in 10 gm, 30 gm and 100 gm sizes.

	TAZORAC™ Gel 0.05%	TAZORAC™ Gel 0.1%
10 gm	NDC 0023-8335-01	NDC 0023-0042-01
30 gm	NDC 0023-8335-03	NDC 0023-0042-03
100 gm	NDC 0023-8335-10	NDC 0023-0042-10

**NOTE:** TAZORAC™ Gel should be stored at  $25^\circ\text{C}$  ( $77^\circ\text{F}$ ): excursion permitted to  $15\text{-}30^\circ\text{C}$  ( $59\text{-}86^\circ\text{F}$ ).

**CAUTION: Federal (U.S.A.) law prohibits dispensing without prescription.**

**ALLERGAN**

Allergan, Inc.

Irvine, California 92612, U.S.A.

January 1997

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Printed in U.S.A

**Pharmacist: Please detach at perforation and provide this patient package insert to your customer.**

**TAZORAC™**  **ALLERGAN**  
**(tazarotene topical gel) 0.05%**  
**(tazarotene topical gel) 0.1%**

#### **INFORMATION FOR PATIENTS**

**Please read this leaflet carefully before you start to use your medicine. If you have any questions, or are not sure about anything, ask your doctor or pharmacist.**

- The active ingredient in TAZORAC™ is tazarotene.
- TAZORAC™ also contains benzyl alcohol as a preservative and the following inactive ingredients: ascorbic acid, butylated hydroxyanisole, butylated hydroxytoluene, carbomer 934P, edetate disodium, hexylene glycol, purified water, poloxamer 407, polyethylene glycol 400, polysorbate 40, and tromethamine.

#### **USES**

TAZORAC™ 0.05% Gel is used in the treatment of stable plaque psoriasis covering up to 20% of body surface area.

TAZORAC™ 0.1% Gel is used in the treatment of stable plaque psoriasis covering up to 20% of body surface area and in the treatment of mild to moderately severe facial acne.

#### **BEFORE YOU USE THIS MEDICINE**

You should be aware that:

- (a) TAZORAC™ should not be used if you are pregnant, attempting to become pregnant or at high risk of pregnancy. Consult your physician for adequate birth control measures if you are a female of child-bearing potential.
- (b) TAZORAC™ should be used with caution if you are also using other topical agents with a strong skin drying effect, products with high concentrations of alcohol, astringents, spices, the peel of lime, medicated soaps or shampoos, permanent wave solutions, electrolysis, hair depilatories or waxes, or other preparations or processes that might dry or irritate the skin, unless otherwise instructed by your health care practitioner.
- (c) TAZORAC™ should not be used if you have sunburn, eczema or other chronic skin condition(s). TAZORAC™ may cause severe irritation if applied to eczematous skin. If you have sunburn, you should wait until full recovery before using TAZORAC™.
- (d) TAZORAC™ should not be used if you are inherently sensitive to sunlight.
- (e) TAZORAC™ should not be used if you are taking other drugs that increase your sensitivity to sunlight. Inform your physician if you are taking any other medications.
- (f) You should use protective clothing and sunscreens with minimum SPF of 15 during the day when being treated with TAZORAC™. You should avoid direct sun exposure as much as possible and avoid sunlamps totally while being treated with TAZORAC™, unless advised otherwise by your doctor.
- (g) If you have considerable sun exposure due to occupation, particular caution as described above should be exercised when using TAZORAC™.
- (h) Weather extremes, such as wind or cold, may be more irritating to your skin while you are using TAZORAC™.

#### **BEFORE YOU USE THIS MEDICINE**

Tell your doctor:

- (a) if you are pregnant or are considering becoming pregnant.
- (b) if you are breast-feeding.
- (c) if you are allergic to any ingredients in this medicine.
- (d) if you are already using other products that make your skin dry.
- (e) if you have a skin condition called eczema.
- (f) if you will be subject to excessive sun exposure.
- (g) if you are taking vitamin A supplements.

#### **HOW TO USE THIS PRODUCT:**

- Read the directions on your prescription label carefully. Ask your doctor or pharmacist to explain

anything that you do not understand.

- If you become pregnant while using TAZORAC™, you should immediately discontinue its use and contact your doctor.
- If you use a cream or lotion to soften or lubricate your skin, apply TAZORAC™ after ensuring that there is no more cream or lotion on the skin.
- After applying TAZORAC™, some people notice a feeling of itching, burning or stinging. This feeling may occur less often as your skin gets used to the medication. Consult your health care provider if increased sensitivity or irritation occurs.
- Do not cover treated areas with dressings or bandages.
- Never use more TAZORAC™ than instructed and never use it more often than instructed, as application of larger amounts of medication than recommended will not lead to more rapid or better results, and marked redness, peeling or discomfort may occur.
- Wash your hands after applying the medication, unless you are treating your hands for psoriasis. If the gel accidentally gets on areas you do not need to treat, wash it off.
- If TAZORAC™ comes in contact with your eyes, wash your eyes with large amounts of cool water, and contact a doctor if eye irritation persists.

#### **MISSED DOSES:**

- If you forget or miss a dose of TAZORAC™, do not try to "make it up." Return to your normal application schedule as soon as you can.

#### **INSTRUCTIONS SPECIFIC TO TREATMENT OF PSORIASIS:**

- If you bathe or shower before using TAZORAC™, be sure the skin is dry before application. Apply a thin film of the gel to your psoriasis lesions once a day before going to bed.
- Carefully avoid application to apparently unininvolved skin. TAZORAC™ may be more irritating to non-lesional skin.
- If you need to treat your hands, avoid contact with your eyes.
- Usually your psoriasis plaques and scales will begin to improve in about one to four weeks but the redness may take longer to improve. Continue to use TAZORAC™ as directed by your doctor.
- Contact your doctor if your psoriasis becomes worse.

#### **INSTRUCTIONS SPECIFIC TO TREATMENT OF ACNE:**

- Gently clean and dry face before using TAZORAC™. Apply TAZORAC™ once a day, before going to bed, to entire areas of the face where you have acne lesions. Use enough gel to cover the entire affected area with a thin film.
- Follow your doctor's directions for other routine skin care and the use of make-up. Talk to your doctor about the use of sunscreens and cosmetics, especially those that dry your skin.
- Usually, your acne will begin to improve in about 4 weeks. Continue to use TAZORAC™ for up to 12 weeks as directed by your doctor.
- Contact your doctor if your acne becomes worse.

#### **WARNINGS:**

TAZORAC™ should not be used if you are pregnant, attempting to become pregnant or at high risk of pregnancy. Women of child-bearing potential should use adequate birth-control measures when TAZORAC™ is used.

If TAZORAC™ is swallowed by accident, contact your doctor or a poison control center.

Do not use TAZORAC™ after the expiration date found on the bottom seal of the tube.

This medicine is for your use only. It can only be prescribed by a doctor. Never give it to anyone else. It may harm them even if their skin problem appears to be the same as yours.

Retinoids should not be used on eczematous skin, as they may cause severe irritation. Do not use TAZORAC™ until your doctor has confirmed that your eczema has fully recovered.

Because of increased burning susceptibility, exposure to sunlight (including sunlamps) should be avoided or minimized during the use of TAZORAC™, unless prescribed differently by your doctor.

You should use sunscreens (minimum SPF of 15) and protective clothing when using TAZORAC™. Be certain that you use these precautions if you expect to experience considerable sun exposure or if you are

sensitive to sunlight.

If you have a sunburn, do not use TAZORAC™ until you have fully recovered.

Do not use TAZORAC™ if you are also taking drugs known to be photosensitizers (e.g., thiazides, tetracyclines, fluoroquinolones, phenothiazines, sulfonamides), unless you have discussed taking both drugs with your doctor, because of the increased possibility of a more severe reaction.

*The safety of use over more than 20% of body surface area has not been established in psoriasis or acne.*

**INSTRUCTIONS FOR USE AND HANDLING:** Keep tube tightly closed when not in use. Store it in a safe place where children cannot reach it. TAZORAC™ Gel should be stored at 25°C (77°F); excursion permitted to 15-30 °C (59-86°F).

**IF YOU HAVE QUESTIONS ABOUT TAZORAC™ Gel:** You may contact Allergan by calling 800-433-8871.

**IF YOU HAVE QUESTIONS ABOUT PSORIASIS:** Information is available from:

The National Psoriasis Foundation:

6600 SW 92nd Avenue, Suite 300, Portland, OR 97223-7195.

Telephone: (800) 723-9166, or on the World Wide Web at <http://www.psoriasis.org>.

**ALLERGAN**

Allergan, Inc.

Irvine, California 92612, U.S.A.

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January 1997

(PM#) (copy code)

Printed in U.S.A.



## DEPARTMENT OF HEALTH &amp; HUMAN SERVICES

Public Health Service

**Division of Dermatologic and Dental Drug Products**

Center for Drug Evaluation and Research  
Food and Drug Administration  
9201 Corporate Boulevard, HFD-540  
Rockville, MD 20850

**FACSIMILE TRANSMISSION**

DATE: June 13, 1997.

Number of Pages (including cover sheet) 15

TO: Thomas Walton  
COMPANY: Allergan  
FAX NUMBER: 714-246-4272

MESSAGE: NDA 20-600 Tazorac Gel

Please find Approval letter and approved labeling for NDA 20-600.

NOTE: We are providing the attached information via telefacsimile for your convenience. This material should be viewed as unofficial correspondence. Please feel free to contact me if you have any questions regarding the contents of this transmission.

FROM: Olga Cintron, R.Ph.  
TITLE: Project Manager  
TELEPHONE: 301-827-2020

FAX NUMBER: 301-827-2075

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW. If you are not the addressee, or a person authorized to deliver the document to the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you have received this document in error, please immediately notify us by telephone and return it to us at the above address by mail. Thank you.

# ATTACHMENT G

Page 41

## STATEMENT IN ACCORDANCE WITH 37 CFR § 1.740(a)(12)

Applicant is of the opinion that U.S. Patent 5,089,509 is eligible for extension under 35 U.S.C. § 156 because it satisfies all the requirements for such extension as follows:

I. (a) 35 U.S.C. § 156(a)

U.S. Patent No. 5,089,509 claims the compound Tazarotene, i.e., 6-[2-(4,4-dimethylthiochroman-6-yl)ethynyl]nicotinate, and the use thereof in treating psoriasis;

(b) 35 U.S.C. § 156(a)(1)

The term of U.S. Patent No. 5,089,509 has not expired before submission of this Application for Extension;

(c) 35 U.S.C. § 156(a)(2)

The term of U.S. Patent No. 5,089,509 has never been extended;

(d) 35 U.S.C. § 156(a)(3)

The Application of Extension is submitted by Allergan the owner of record of U.S. Patent No. 5,089,509 in accordance with the requirements of 35 U.S.C. § 156(d) and the guidelines of the United States Patent and Trademark Office;

(e) 35 U.S.C. § 156(a)(4)

Tazorac<sup>®</sup> having the active ingredient Tazarotene, has been subject to a regulatory review period for its commercial marketing or use;

## **ATTACHMENT G (cont'd)**

Page 42

- (f) 35 U.S.C. § 156(a)(5)(A)

The permission for commercial marketing or use of Tazorac®, after the regulatory review period is the first permitted commercial marketing or use of Tazarotene, the active ingredient under the provision of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355), under which such regulatory review period occurred; and

- (g) 35 U.S.C. § 156(c)(4)

No other patent has been extended for the same regulatory period for the the active ingredient Tazarotene.

II. The length of extension of the patent term of U.S. Patent 5,089,509 claimed by applicant is 845 days or 2.3 years, which will have the effect of extending the term of the patent after the date of approval of Tazorac® to fourteen (14) years in accordance with 35 USC § 156(c)(3).

- (a) The regulatory review period under 35 U.S.C. § 156(g)(1)(B) was from February 16, 1990 (the effective date of the IND) until June 13, 1997 which is 2,674 days or 7.3 years.

- (b) The period of review, under 35 U.S.C. § 156(g)(1)(B)(i) was from February 16, 1990 (effective date of IND) until June 16, 1995 (NDA submission date), which is 1,946 days or 5.3 years.

- (c) The period of new drug application review under 35 U.S.C. § 156(g)(B)(ii) was from June 16, 1995 (NDA submission date) until June 13, 1997 (NDA approval date), which is 730 days or 2.0 years.

## **ATTACHMENT G (cont'd)**

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- (d) Under 35 U.S.C. § 156 (c)(2), the period of extension may include only one half of the period determined under 35 U.S.C. § 156(g)(1)(B)(i), i.e., 1337 days or 3.7 years (as per II(b) above).
- (e) In compliance with 35 U.S.C. § 156(c)(3), the period remaining in the term of U.S. Patent No. 5,089,509 after NDA approval of Tazorac® i.e., from June 13, 1997 to February 18, 2009, i.e. 4,268 days or 11.7 years, which period does not exceed fourteen (14) years.



DOCKET NO. 16561CIP1(HL)

PATENT

AUG 11 1997  
THE UNITED STATES PATENT AND TRADEMARK OFFICE

PATENT & TRADEMARK OFFICE  
Re: U.S. Patent No. 5,089,509

Issued: February 18, 1992

To: Roshantha Chandraratna

For: DISUBSTITUTED ACETYLENES BEARING  
HETEROAROMATIC AND HETEROBICYCLIC  
GROUPS HAVING RETINOID LIKE ACTIVITY

August 11, 1997

RECEIVED

Commissioner of Patents and Trademarks  
Box Patent Extension  
Washington, D.C. 20231

MAR - 2 1998

PATENT EXTENSION  
A/C PATENTS

DECLARATION

Sir:

The undersigned, Attorney for Allergan, which is the applicant for extension of patent term under 35 U.S.C. 156 with respect to U.S. Patent No. 5,089,509, hereby declares that:

(1) He is a patent attorney authorized to practice before the Patent and Trademark Office and has the general authority from the Applicant to act on its behalf in patent matters. (See attached power of attorney.)

(2) He has reviewed and understands the contents of the application being submitted pursuant to 35 U.S.C. § 156 and 37 CFR § 1.740.

(3) He believes the patent is subject to extension pursuant to 37 CFR § 1.710;

(4) He believes an extension of the length claimed is fully justified under 35 U.S.C. § 156 and the applicable regulations; and

(5) He believes the patent for which the extension is being sought meets the conditions for extension of the term of a patent as set forth in 35 U.S.C. § 156 and 37 CFR § 1.720.

The undersigned hereby declares further that all statements made herein of his own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any extension of patent term issuing thereon.

Date: Aug 11, 1997

RJ Baran  
Robert J. Baran

CERTIFICATE OF MAILING

I HEREBY CERTIFY THAT THIS CORRESPONDENCE IS BEING DEPOSITED WITH THE UNITED STATES POSTAL SERVICE WITH SUFFICIENT POSTAGE AS EXPRESS MAIL IN AN ENVELOPE ADDRESSED TO: BOX PATENT EXTENSION, ASSISTANT COMMISSIONER FOR PATENTS, WASHINGTON, D.C. 20231 ON August 11, 1997 (Date)

Name of person making deposit: Bonnie Ferguson

Signature: Bonnie Ferguson Date 8/11/97

Attorney's Docket No. 16561-CIP-1

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE  
71435

In Re Patent Off AUG 1 1997 )  
Inventor: Roshantha A. Chandraratne ) Group No.:  
For: DISUBSTITUTED ACETYLENES ) Examiner:  
BEARING HETEROAROMATIC )  
AND HETEROBICYCLIC GROUPS )  
HAVING RETINOID LIKE )  
ACTIVITY )  
Patent No: 5,089,509 ) Issued: February 18, 1992  
Date: August 7, 1997

Assistant Commissioner for Patents  
Washington, D.C. 20231

POWER OF ATTORNEY BY ASSIGNEE OF ENTIRE INTEREST

As assignee of record of the entire interest of the above identified

application,

patent,

POWER OF ATTORNEY

the following attorney is hereby appointed to prosecute and transact  
all business in the Patent and Trademark Office connected therewith.

Robert J. Baran

Registration No. 25,806

SEND CORRESPONDENCE TO: DIRECT TELEPHONE CALLS TO:

Robert J. Baran (714) 246-4669  
c/o Allergan, Inc.  
2525 Dupont Drive, T-2;2-E  
Post Office Box 19534  
Irvine, CA 92623-9534

ALLERGAN

(type or print identity of assignee  
of entire interest)

2525 Dupont Drive, T-2; 2-E  
Address

P. O. Box 19534

Irvine, CA 92623-9534

Recorded in PTO on May 6, 1996

Reel 8239

Frame 0239

Recorded herewith

**ASSIGNEE CERTIFICATION**

Attached to this power is a "CERTIFICATE UNDER 37 CFR 3.73(b)."

Martin A. Voet  
Signature

Date: August 7, 1997

Martin A. Voet  
(type or print name of person  
authorized to sign on behalf  
of assignee)  
Assistant Secretary of Allergan, Inc.  
General Partner of Allergan  
Title

CERTIFICATE UNDER 37 CFR 3.73(b)

Assistant Secretary of Allergan, Inc.

I, MARTIN A. VOET, General Partner of Allergan, have reviewed the assignment documents and certify, to the best of his knowledge and belief, Allergan, i.e. the party seeking to extend the patent term of U.S. Patent No. 5,089,509, is the assignee of the entire right, title and interest of U.S. Patent No. 5,089,509.

DATE: August 7, 1997

ALLERGAN

By:

  
Martin A. Voet